| | |
|---|---|
| **Official Protocol Title:** | A Phase I, Double-Blind, Randomized, Multicenter Trial of the Safety, Tolerability, and Immunogenicity of V114 in Healthy Japanese Infants |
| **NCT number:** | NCT03848065 |
| **Document Date:** | 12-Dec-2018 |

# Title Page

**THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., NJ, U.S.A. (MSD).**

**Protocol Title:** A Phase I, Double-Blind, Randomized, Multicenter Trial of the Safety, Tolerability, and Immunogenicity of V114 in Healthy Japanese Infants

**Protocol Number:** 028-00

**Compound Number:** V114

**Sponsor Name:**

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

**Legal Registered Address:**

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

**Regulatory Agency Identifying Number(s):**

| | |
|---|---|
| IND | Not Applicable |

**Approval Date: 12-December-2018**

## Sponsor Signatory

Typed Name:
Title:

Date

**Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).**

## Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

# Table of Contents

# LIST OF TABLES

# LIST OF FIGURES

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:** A Phase I, Double-Blind, Randomized, Multicenter Trial of the Safety, Tolerability, and Immunogenicity of V114 in Healthy Japanese Infants

**Short Title:** Safety and Immunogenicity of V114 in Healthy Japanese Infants

**Acronym:** Not applicable

**Hypotheses, Objectives, and Endpoints:**

There is no formal hypothesis in this study.

The following objectives and endpoints will be assessed in healthy Japanese infants.

| Primary Objectives | Primary Endpoints |
|---|---|
| · **Objective:** To describe the safety and tolerability profiles of V114 given subcutaneously (V114-SC) and V114 given intramuscularly (V114-IM) in healthy infants. | · Solicited injection-site adverse events (AEs) during Day 1 to Day 14 postvaccination<br>· Solicited systemic AEs during Day 1 to Day 14 postvaccination<br>· Vaccine-related serious adverse events (SAEs) during Day 1 to 1 month post-Dose 4 (PD4) |
| Secondary Objectives | Secondary Endpoints |
| · **Objective:** To assess the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 1 month post-Dose 3 (PD3) for each vaccination group. | · Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 1 month PD3 |
| · **Objective:** To assess the anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) at 1 month PD3 for each vaccination group. | · Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 1 month PD3 |

| | |
|---|---|
| • **Objective:** To assess the proportion of participants meeting threshold values* for protective responses to DTaP-IPV (Diphtheria toxin, Tetanus toxin, Pertussis toxin, Pertussis filamentous hemagglutinin (FHA), and Polio virus type 1/2/3) at 1 month PD3 for each vaccination group.<br>Threshold value*: Diphtheria toxin level ≥0.1 IU/mL, Pertussis PT level ≥10 EU/mL Pertussis FHA level ≥10 EU/mL, Tetanus toxin level ≥0.01 IU/mL, Neutralizing antibody titers (NA) of Polio virus type 1/2/3 ≥1:8 | • The antibody responses for DTaP-IPV at 1 month PD3 |

**Overall Design:**

| | |
|---|---|
| Study Phase | Phase 1 |
| Primary Purpose | Prevention |
| Indication | Pneumococcal disease |
| Population | Healthy Japanese infants |
| Study Type | Interventional |
| Intervention Model | Parallel<br>This is a multi-site study. |
| Type of Control | Active control without placebo |
| Study Blinding | Double-blind |
| Masking | Participant or Subject<br>Care Provider<br>Investigator<br>Sponsor |
| Estimated Duration of Study | The Sponsor estimates that the study will require approximately 2 years from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.<br>For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last serology assay result or at the time of final contact with the last participant, whichever comes last. |

## Number of Participants:

Approximately 120 participants will be randomized (40 participants/group), estimating with 36 evaluable participants complete the study in each group.

## Intervention Groups and Duration:

Intervention Groups

| Intervention Group Name | Vaccine | Dose Strength | Dose Frequency | Route of Admin. | Vaccination Regimen | Use |
|---|---|---|---|---|---|---|
| V114-SC | V114 | Refer to IB | 4 doses | SC | Single dose at Visit 1, 2, 3 and 5* (Approximately 3, 4, 5, and 12 to 15 months of age). | Experimental |
| V114-IM | V114 | Refer to IB | 4 doses | IM | Single dose at Visit 1, 2, 3 and 5* (Approximately 3, 4, 5, and 12 to 15 months of age). | Experimental |
| PCV13-SC | PCV13 | Refer to product labeling | 4 doses | SC | Single dose at Visit 1, 2, 3 and 5* (Approximately 3, 4, 5, and 12 to 15 months of age). | Experimental |

Admin: Administration, PCV13: Pneumococcal 13-valent Conjugate Vaccine, IB: Investigator's Brochure, IM: Intramuscular, SC: Subcutaneous

* DTaP-IPV (Diphtheria, tetanus, acellular pertussis, inactivated polio vaccine) is administrated with V114/PCV13 concomitantly at Visit 1, 2, 3 and 5.

| | |
|---|---|
| Total Number | 3 intervention groups |
| Duration of Participation | Each participant will participate in the study for approximately 10-14 months, from the time the parent/legal guardian signs the Informed Consent Form (ICF) through the final contact. |

**Study Governance Committees:**

| | |
|---|---|
| Steering Committee | No |
| Executive Oversight Committee | No |
| Data Monitoring Committee | No |
| Clinical Adjudication Committee | No |
| Study governance considerations are outlined in Appendix 1. | |

**Study Accepts Healthy Volunteers:** Yes

A list of abbreviations used in this document can be found in Appendix 8

## 1.2 Schema

The study design is depicted in Figure 1.

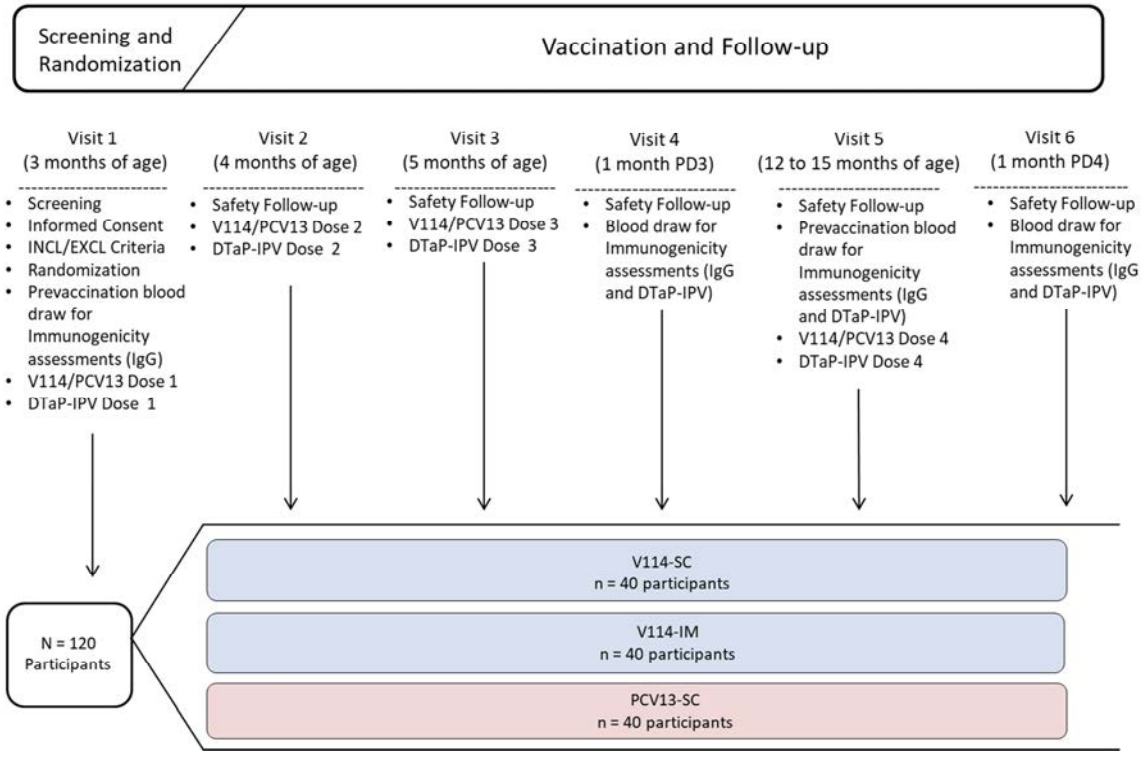


Figure 1 V114-028 Study Design

## 1.3 Schedule of Activities (SoA)

| **Study Period** | **Screening** | **Intervention** | | | | | **Notes** |
|---|---|---|---|---|---|---|---|
| **Visit Number** | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** | |
| **Standard Age/ Scheduled Time** | **3 months** | **4 months** | **5 months** | **1 month PD 3** | **12~15 months** | **1 month PD 4** | The age of the subject will fall within the appropriate age range for each trial visit. |
| | **DOSE 1** | **DOSE 2** | **DOSE 3** | **POST DOSE 3** | **DOSE 4** | **POST DOSE 4** | |
| **Visit Window** | **3 months of age to 1 day prior to 4months of age** | **28 to 42 days after Visit 1** | **28 to 42 days after Visit 2** | **28 to 42 days after Visit 3** | **12 months of age to 1 day prior to 16 months of age** | **28 to 42 days after Visit 5** | Months of age is calculated according to the participant's birth date. |
| **Screening Procedures** | | | | | | | |
| Informed Consent | X | | | | | | Consent must be obtained before any study procedures. |
| Informed Consent for Future Biomedical Research (FBR) | X | | | | | | Consent for FBR samples is optional and must be obtained before the collection of the buccal swab DNA samples. |
| Assignment of Screening Number | X | | | | | | |
| Participant Identification Card | X | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | |
| Medical History | X | | | | | | The participant's medical history from the birth to first vaccination will be reviewed. |
| **Post-enrollment procedures** | | | | | | | |
| Assignment of Randomization Number | X | | | | | | |
| Prior/Concomitant Medication and Nonstudy Vaccination Review | X | X | X | X | X | X | See Section 8.1.5 for details. |

| **Study Period** | **Screening** | **Intervention** | | | | | **Notes** |
|---|---|---|---|---|---|---|---|
| **Visit Number** | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** | |
| **Standard Age/ Scheduled Time** | **3 months** | **4 months** | **5 months** | **1 month PD 3** | **12~15 months** | **1 month PD 4** | The age of the subject will fall within the appropriate age range for each trial visit. |
| | **DOSE 1** | **DOSE 2** | **DOSE 3** | **POST DOSE 3** | **DOSE 4** | **POST DOSE 4** | |
| **Visit Window** | **3 months of age to 1 day prior to 4months of age** | **28 to 42 days after Visit 1** | **28 to 42 days after Visit 2** | **28 to 42 days after Visit 3** | **12 months of age to 1 day prior to 16 months of age** | **28 to 42 days after Visit 5** | Months of age is calculated according to the participant's birth date. |
| V114 or PCV13 Administration (Blinded) | X | X | X | | X | | Due to differences in appearance, vaccine administration will be performed by unblinded trial personnel who will have no contact with study participants other than for administration of study vaccine. This includes all safety follow-up procedures (Section 6.3.3). |
| Concomitant Vaccine (DTaP-IPV) Administration | X | X | X | | X | | DTaP-IPV is administrated with V114/PCV13 concomitantly. |
| Nonstudy Pediatric Vaccines | (X) | (X) | (X) | (X) | (X) | (X) | Injectable vaccines should not be administrated in the same limb as the study vaccine. |
| Provide Vaccination Report Card (VRC) | X | X | X | | X | | See Section 8.1.9 for details. |
| VRC Collection | | X | X | X | | X | |
| Review VRC data | | X | X | X | | X | |
| **Immunogenicity Procedures** | | | | | | | |
| Collect Blood Samples for IgG Immunogenicity Assays | X* | | | X | X* | X | *Prior to vaccination |
| Collect Blood Samples for DTaP-IPV Immunogenicity Assays | | | | X | X* | X | *Prior to vaccination |

| **Study Period** | **Screening** | **Intervention** | | | | | **Notes** |
|---|---|---|---|---|---|---|---|
| **Visit Number** | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6** | |
| **Standard Age/ Scheduled Time** | **3 months** | **4 months** | **5 months** | **1 month PD 3** | **12~15 months** | **1 month PD 4** | The age of the subject will fall within the appropriate age range for each trial visit. |
| | **DOSE 1** | **DOSE 2** | **DOSE 3** | **POST DOSE 3** | **DOSE 4** | **POST DOSE 4** | |
| **Visit Window** | **3 months of age to 1 day prior to 4months of age** | **28 to 42 days after Visit 1** | **28 to 42 days after Visit 2** | **28 to 42 days after Visit 3** | **12 months of age to 1 day prior to 16 months of age** | **28 to 42 days after Visit 5** | Months of age is calculated according to the participant's birth date. |
| **Safety Procedures** | | | | | | | |
| Full Physical Examination | X | | | | | | To be performed by the investigator before vaccination to check inclusion/exclusion criteria/eligibility. |
| Targeted Physical Examination | | X | X | | X | | To be performed by the investigator before vaccination. |
| Weight | X | | | | | | |
| Body Temperature Measurement | X | X | X | | X | | Pre-vaccination body temperatures measured by site staff. (See section 8.3.2 for details) |
| 30 Minutes Post Vaccination Observation Period | X | X | X | | X | | Subjects will be observed after study vaccination by blinded study personnel only. |
| AE Monitoring | ←==========→ | | | | | | Nonserious AEs are to be reported from Days 1 through 14 following each vaccination. SAEs and deaths are to be reported throughout the duration of an individual's study participation. |
| **Future Biomedical Research** | | | | | | | |
| Collect Buccal Swabs for Future Biomedical Research | X | | | | | | Collected from randomized participants who provided consent for FBR (Section 8.8) |

# 2 INTRODUCTION

Merck Sharp & Dohme Corp. (MSD) is developing an investigational 15-valent pneumococcal conjugate vaccine (PCV) (referred to as V114) for the prevention of pneumococcal disease (PD) caused by the serotypes in the vaccine. V114 contains the 13 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) present in the licensed vaccine PCV13 (pneumococcal 13-valent conjugate vaccine [diphtheria $CRM_{197}$ protein], Wyeth Pharmaceuticals, a subsidiary of Pfizer, Inc., Philadelphia, PA), plus 2 additional serotypes (22F, 33F).

## 2.1 Study Rationale

*Streptococcus pneumoniae* is a major cause of morbidity and mortality in children (< 5 years of age) and older adults (≥ 65 years of age) worldwide [Cherian T 2007]. PD continues to be a leading cause of vaccine preventable disease worldwide and remains an unmet medical need despite the significant public health impact of currently available PCVs. Since the introduction of multi-valent PCVs, the overall burden of PD has decreased significantly. However, the absolute and proportional burden of disease due to non-vaccine serotypes has increased in regions where multi-valent PCVs have been introduced into infant immunization schedules. Vaccinated and unvaccinated individuals remain susceptible to disease caused by non-vaccine serotypes.

In 2016, data from United States (US) Centers for Disease Control and Prevention (CDC) showed that serotypes 22F and 33F accounted for ~16% of all Invasive Pneumococcal disease (IPD) cases in children <5 years of age. In Japan, the rate of serotypes 22F and 33F isolates from children <15 years with IPD in 2014 were 11.1% and 0.8% [Nakano S., et al 2016]. Both 22F and 33F have been associated with serious clinical outcomes, including IPD, as demonstrated by their high degree of invasiveness compared with other serotypes not currently covered by licensed PCVs. Furthermore, serotypes 22F and 33F have shown relative resistance to certain antibiotics used in the treatment of community acquired pneumonia [Golden AR.,et al 2016]. Thus, it is anticipated that vaccination with V114 will contribute further to prevention of disease in both children and adults due to clinically important strains of *S. pneumoniae* compared to PCV13.

This clinical study is designed to describe the safety, tolerability, and immunogenicity of V114 administered subcutaneously or intramuscularly in healthy Japanese infants (3 months of age).

## 2.2 Background

Refer to the Investigator's Brochure (IB) for detailed background information on V114.

Pneumococcal infection is a major cause of pneumonia, bacteremia, and meningitis. Data from the Active Bacterial Core Surveillance (ABCS) network of the US CDC over the past 12 years have clearly shown that IPD, including meningitis, bacteremia without focus, and pneumonia with bacteremia, is a major public health problem in children and adults [Pilishvili T., et al 2010] [Robinson KA., et al 2001] [Centers for Disease Control and Prevention 1997] [Centers for Disease Control and Prevention 2016]. Infection surveillance in Japan (2017) indicates that the total number of reports of IPD was 3,139, and prevalence was 9.37 per 100,000 population for children <5 years of age and 5.34 per 100,000 population for adults 65 years of age and older.

Although all age groups could be affected by IPD, the highest rates of disease occur in young children <5 years of age and adults ≥65 years of age [Chiba N., et al 2014]. The majority of disease has traditionally occurred in young children. However, with the universal adoption of PCV7 (Pneumococcal 7-valent Conjugate Vaccine [Diphtheria $CRM_{197}$ Protein], Pfizer) the incidence of IPD in children <5 years of age in the U.S. declined significantly from 98.7 per 100,000 population in 1998 to 20.2 per 100,000 population in 2008, and then 12.0 per 100,000 population in 2011. (7-valent Conjugate Vaccine is also known as Prevenar™/ Prevnar™ in many countries and will be referred to as PCV7 throughout this document.)

In Japan, PCV7 vaccination was introduced for children <5 years of age in November 2010 by the Provisional Fund for the Urgent Promotion of Vaccination. PCV7 was incorporated into routine vaccination schedules in April 2013. PCV7 rapidly decreased IPD infections in children. However, pneumococcal infections caused by non-PCV7 serotypes (19A, 15A, 15B, 15C, and 24F) increased in children during 2012 [Nakano S., et al 2016].

Subsequent to PCV7, new PCVs were developed to address the increase in IPD caused by these emergent serotypes. The 13-valent PCV was approved in the EU in 2009, the U.S. in 2010, and Japan in 2013. (This vaccine is licensed globally as Prevenar 13™ /Prevnar 13™, and will be referred to as PCV13 in this protocol.) Similar to PCV7, all 13 serotypes in PCV13 are conjugated with diphtheria $CRM_{197}$ carrier protein. The widespread use of PCV13 in infants has further decreased the incidence of IPD caused by the original serotypes in PCV7 but also disease caused by the majority of the additional 6 serotypes included unique to PCV13.

Despite these significant advances, serotype replacement remains a concern as new serotypes begin to fill the niche created by the suppression of nasopharyngeal colonization of vaccine serotypes. In particular, serotypes 22F and 33F, the 2 additional serotypes contained in V114 contributed in 1998 to approximately 1.3% of overall IPD in U.S. children under 5 years of age [Pilishvili T., et al 2010], but have now been estimated to represent ~16% of all IPD cases in this age group in 2016.

In Japan, since April 2013, PCV7 has become a routine vaccine and was replaced by PCV13 in November 2013. Recently, the vaccination rate has reached nearly 100% and serotypes 22F and 33F contributed to approximately 12 % of overall IPD in children under 15 years of age in 2014.

### 2.2.1 Pharmaceutical and Therapeutic Background

#### 2.2.1.1 V114

The investigational Merck Sharp & Dohme Corp. (MSD), PCV15 (V114) is a 15-valent vaccine, containing pneumococcal polysaccharide conjugates of the 13 serotypes in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, and 23F) plus 2 additional serotypes (22F and 33F). V114 contains 32 µg of polysaccharides (2 µg for each serotype except serotype 6B which is present at 4 µg), 32 µg of $CRM_{197}$ carrier protein, and 125 µg of aluminum phosphate adjuvant (APA). In clinical studies conducted outside Japan, V114 has been administered intramuscularly to healthy adults 18 to 49 years of age, healthy adults 50 years of age and older and infants 6 to 12 weeks of age. In a clinical study conducted in Japan, V114 has been administered intramuscularly to healthy adults 50 years of age and older. There are no significant safety findings or issues related to V114 in clinical studies to date. Please refer to the IB on V114.

### 2.2.2 Preclinical and Clinical Studies

Refer to the IB for information on the preclinical and clinical studies conducted with V114.

### 2.2.3 Information on Other Study-related Therapy

#### 2.2.3.1 PCV13 (Prevenar 13™/ Prevnar 13™)

Refer to approved labeling for detailed background information on PCV13.

PCV13 contains the 7 pneumococcal serotypes included in PCV7 (4, 6B, 9V, 14, 18C, 19F, 23F) plus 6 additional serotypes (1, 3, 5, 6A, 7F, and 19A). PCV7 and PCV13 are also known as Prevenar™/ Prevnar™ and Prevenar 13™ /Prevnar 13™ in many countries; these vaccines will be referred to as PCV7 and PCV13 throughout this document.

#### 2.2.3.2 DTaP-IPV vaccine

Refer to approved labeling for detailed background information on DTaP-IPV vaccine administered concomitantly. Licensed DTaP-IPV vaccines will be provided and administered concomitantly according to the recommended schedule.

## 2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

A subset of subjects will receive 4 dose of PCV13 which is the standard of care and is serving as the active comparator in this trial. V114 is expected to provide comparable immune responses and safety profile to PCV13 for the shared pneumococcal serotypes while

providing additional coverage for the 2 serotypes (22F and 33F) unique to V114. It is unknown if the investigational V114 will have the same benefit as PCV13.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

# 3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

There is no formal hypothesis testing in this study.

The following objectives and endpoints will be assessed in healthy Japanese infants 3 months of age.

| Primary Objectives | Primary Endpoints |
|---|---|
| · **Objective:** To describe the safety and tolerability profiles of V114 given subcutaneously (V114-SC) and V114 given intramuscularly (V114-IM) in healthy infants. | · Solicited injection-site adverse events (AEs) during Day 1 to Day 14 postvaccination<br>· Solicited systemic AEs during Day 1 to Day 14 postvaccination<br>· Vaccine-related serious adverse events (SAEs) during Day 1 to 1 month post-Dose 4 (PD4) |
| Secondary Objectives | Secondary Endpoints |
| · **Objective:** To assess the anti-pneumococcal polysaccharide (PnPs) serotype-specific Immunoglobulin G (IgG) response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) at 1 month post-Dose 3 (PD3) for each vaccination group. | · Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 1 month PD3 |
| · **Objective:** To assess the anti-PnPs serotype-specific IgG Geometric Mean Concentrations (GMCs) at 1 month PD3 for each vaccination group. | · Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at 1 month PD3 |

| | |
|---|---|
| • **Objective:** To assess the proportion of participants meeting threshold values* for protective responses to DTaP-IPV (Diphtheria toxin, Tetanus toxin, Pertussis toxin, Pertussis filamentous hemagglutinin (FHA) and Polio virus type 1/2/3) at 1 month PD3 for each vaccination group.<br>Threshold value*: Diphtheria toxin level ≥0.1 IU/mL, Pertussis PT level ≥10 EU/mL, Pertussis FHA level ≥10 EU/mL, Tetanus toxin level ≥0.01 IU/mL, Neutralizing antibody titers (NA) of Polio virus type 1/2/3 ≥1:8 | • The antibody responses for DTaP-IPV at 1 month PD3 |
| Tertiary/Exploratory Objectives | Tertiary/Exploratory Endpoints |
| • **Objective:** To assess the anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 μg/mL) at pre-Dose 4 and 1 month PD4 for each vaccination group. | • Serotype-specific IgG responses for the 15 serotypes contained in V114 at pre-Dose 4 and 1 month PD4 |
| • **Objective:**To assess the anti-PnPs serotype-specific IgG GMCs at pre-Dose 4 and 1 month PD4 for each vaccination group. | • Anti-PnPs serotype-specific IgG responses for the 15 serotypes contained in V114 at pre-Dose 4 and 1 month PD4 |
| • **Objective:**To assess the proportion of participants meeting threshold values for protective responses to DTaP-IPV at pre-Dose 4 and 1 month PD4 for each vaccination group. | • The antibody responses for DTaP-IPV at pre-Dose 4 and 1month PD4 |
| • **Objective:**To assess the geometric mean titers (GMTs) for DTaP-IPV at 1 month PD3, pre-Dose 4 and 1month PD4 for each vaccination group. | • The antibody responses for DTaP-IPV at 1 month PD3, pre-Dose4 and 1month PD4 |

# 4 STUDY DESIGN

## 4.1 Overall Design

This is a multicenter, randomized, double-blind trial of the safety, tolerability, and immunogenicity of 2 different administration routes of V114 (subcutaneous [SC] or intramuscular [IM]) in healthy Japanese infants to be conducted in conformance with Good Clinical Practices (GCPs). PCV13 will be given with SC as the active control.

This trial will enroll approximately 120 healthy Japanese infants 3 months of age. Subjects will be randomly assigned to receive V114-SC (n=40), V114-IM (n=40) or PCV13-SC (n=40). A 0.5 mL subcutaneous or intramuscular dose of the study vaccine will be administered to healthy infants at approximately 3, 4, 5, and 12 to 15 months of age. National Immunization Program (NIP) vaccine of DTaP-IPV (vaccine that protects against diphtheria, tetanus, pertussis and polio) will be administered at the same time as the study vaccine. Although PCV13 is indicated for healthy infants from 2 months of age in Japan and V114 is able to be administered at 2 months of age, study drug (V114 or PCV13) will be administered from 3 months of age in this trial to align with the schedule of DTaP(-IPV), which is indicated for healthy infants from 3 months of age in Japan.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

## 4.2 Scientific Rationale for Study Design

This is a Phase I study to assess the safety, tolerability and immunogenicity of V114 in healthy Japanese infant. PCV13 is indicated for healthy infants from 2 months to 5 years of age in Japan with official funding (NIP) since 2013.

Although SC route is typically selected for most pediatric vaccines in Japan, IM route is needed especially for infants in which the injection sites are limited based on the statement from Japan pediatric society which suggested that IM route was desirable in terms of lower frequency of injection-site AEs and generally better immunogenicity compared with SC [Japan Pediatric Society 2014], and hence the safety and immunogenicity in both routes of V114 will be assessed in this study. In addition, the potential impact of V114 administration on the immune response to concomitant DTaP-IPV will be assessed secondary and exploratory in this study per Japanese regulation to assess the effects of V114 on the immunologenicity and safety for simultaneous vaccinations.

Study results will provide necessary information about the safety and immunogenicity profiles of V114 in Japanese infants before evaluation in subsequent phases of V114 clinical development in Japanese pediatric.

### 4.2.1 Rationale for Endpoints

#### 4.2.1.1 Immunogenicity Endpoints

Serotype-specific IgG

Sera from participants will be used to measure vaccine-induced serotype-specific IgG for all 15 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23, and 33F) included in V114 using the pneumococcal electrochemiluminescence (PnECL) assay. Anti-PnPs serotype-specific IgG responses will be measured at baseline, 1 month PD3 for infant series (primary series), pre-Dose 4 for toddler (booster) to evaluate the anamnestic antibody responses and the persistence of protective immunity and 1 month PD4 for booster to measure the responses after Dose 4.

Immunogenicity endpoints for the comparison of PCVs in children are based on IgG antibodies responses. Such responses are consistent with the recommendations from the World Health Organization (WHO) and many regulatory agencies worldwide and include serotype-specific measurements of the following endpoints: a) the proportion of subjects achieving IgG antibody concentrations ≥0.35 μg/mL 4 weeks after third dose; and b) the IgG GMCs measured 4 weeks after the third and fourth doses.

Immunogenicity of DTaP-IPV

For the objectives, the immunogenicity endpoint is the proportion of subjects meeting threshold values for protective responses to diphtheria toxin, pertussis toxin, pertussis FHA, tetanus toxin, and polio virus type 1/2/3 at 1 month PD3, pre-Dose 4 and 1month PD4. The infection control threshold levels of responses to DTaP-IPV are defined as shown in Table 1 based on the WHO [World Health Organization 2017-1] [World Health Organization 2017-2], Japanese infection survey [Ministry of Health, Labor and Welfare., et al 2013] and clinical findings [Plotkin SA. 2010][Kato T.1990].

Table 1 Threshold levels of protective responses to DTaP-IPV

| DTaP-IPV | Diphtheria Toxin | Tetanus Toxin | Pertussis Toxin | Pertussis FHA | Polio Type 1 | Polio Type 2 | Polio Type 3 |
|---|---|---|---|---|---|---|---|
| Infection control threshold level | ≥0.1 IU/mL | ≥0.01 IU/mL | ≥10 EU/mL | ≥10 EU/mL | NA≥1:8 | NA≥1:8 | NA≥1:8 |
| FHA: filamentous hemagglutinin, NA: Neutralizing antibody titers (dilution) | | | | | | | |

In addition, the endpoints also include evaluation of the GMTs for components of DTaP-IPV measured at 1 month PD3, pre-Dose 4 and 1 month PD4.

#### 4.2.1.2 Safety Endpoints

The safety endpoints described in this study were selected based on the product's safety profile demonstrated in previous studies and published data from marketed PCVs and feedback received from regulatory agencies during product development.

The participant's parent/guardian will utilize a paper Vaccination Report Card (VRC) to document the following:

- Axillary body temperatures that will be measured on Day 1 (day of vaccination) through Day 7 following each vaccination.
- Solicited injection-site AEs (redness, swelling, hard lump and pain/tenderness) from Day 1 through Day 14 following each postvaccination.
- Solicited systemic AEs (irritability, drowsiness, hives/welts, appetite loss) from Day 1 through Day 14 following each postvaccination.
- Any other injection-site or systemic AEs from Day 1 through Day 14 following each postvaccination.
- Serious AEs will be collected from the time the consent form is signed through completion of the subject's participation in the study (until 1 month PD4)

All participants will be observed for 30 minutes after receipt of the study vaccine for any immediate reactions. The investigator (or medically-qualified designee) will assess the vaccine relatedness of all serious and non-serious AEs, the intensity of all serious and non-serious AEs. During the VRC-specified safety follow-up period (Day 1 through Day 14 of each study vaccination), clinical adverse events will be recorded on the VRC by the participant's parent/guardian on the day of occurrence. The investigator will use the information provided by the participant's parent/guardian both on the VRC, and verbally at the time of VRC review.

#### 4.2.1.3 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that

participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research substudy are presented in Appendix 6.

### 4.2.2 Rationale for the Use of Comparator/Placebo

Placebo-controlled clinical studies for new PCVs are no longer acceptable given the proven clinical efficacy, public health impact, and widespread use of licensed PCVs worldwide. PCV13 is currently the only recommended vaccine for the prevention of pneumococcal disease in Japanese infants and is also used in many other countries worldwide. It will be used as the active comparator in this study.

## 4.3 Justification for Dose

The dose and dosing schedule of V114 is similar to that used in previous pediatric V114 clinical studies, which demonstrated safety and comparable immune responses to those of PCV13. Refer to the V114 IB for details on dosing schedule.

## 4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory assay result or at the time of final contact with the last participant, whichever comes last.

### 4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or an unacceptably high number of discontinuations or withdrawals due to administrative reasons.

# 5 STUDY POPULATION

Healthy male and female participants of 3 months of age will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

1. Be healthy (based on a review of medical history and physical examination) based on the clinical judgment of the investigator.

### Demographics

2. Be male or female 3 months of age inclusive (3 months of age to1 day prior to 4 months of age), at the time of obtaininig the informed consent.

### Informed Consent

3. Have a legally acceptable representative who understands the study procedures, alternate treatments available, and risks involved with the study and voluntarily agrees to participate by giving written informed consent. The legally acceptable representative may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

## 5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

### Medical Conditions

1. Has a history of invasive pneumococcal disease (positive blood culture, positive cerebrospinal fluid culture, or other sterile site) or known history of other culture positive pneumococcal disease.

2. Has a known hypersensitivity to vaccines, any component of the pneumococcal conjugate vaccine or any diphtheria toxoid-containing vaccine

3. Has any contraindication to the PCV13 and/or DTaP-IPV vaccine being administered in the study (Refer to approved labeling for contraindication details on PCV13 and DTaP-IPV vaccine).

4. *Has a recent febrile illness (axillary temperature ≥37.5°C) occurring within 72 hours prior to receipt of study vaccine.

5. Has a known or suspected impairment of immunological function.

6. Has a history of congenital or acquired immunodeficiency.

7. Has or his/her mother has a documented hepatitis B surface antigen – positive test.

8. Has a known functional or anatomic asplenia.

9. Has failure to thrive based on the clinical judgement of the investigator.

10. Has thrombocytopenia or a known coagulation disorder contraindicating intramuscular vaccination.

11. Has a history of autoimmune disease (including but not limited to systemic lupus erythematosus, antiphospholipid syndrome, Bechet's disease, autoimmune thyroid disease, polymyositis and dermatomyositis, scleroderma, type 1 diabetes mellitus, or other autoimmune disorders).

12. Has a known neurologic or cognitive behavioral disorder, including encephalitis/myelitis, acute disseminating encephalomyelitis, pervasive development disorder, and related disorders.

**Prior/Concomitant Therapy**

13. Has received a dose of any pneumococcal and/or DTaP-IPV vaccine (or vaccine containing any DTaP-IPV component) prior to study entry.

14. *Meets one or more of the following systemic corticosteroid exclusion criteria:

    - Has received systemic corticosteroids (equivalent of ≥ 2 mg/kg total daily dose of prednisone or ≥ 20 mg/d for persons weighing > 10 kg) for ≥ 14 consecutive days and has not completed this course of treatment at least 30 days prior to trial randomization.

    - Has received systemic corticosteroids within 14 days prior to the first dose of study vaccine at randomization.

    - Is expected to require systemic corticosteroids (equivalent of ≥ 2 mg/kg total daily dose of prednisone or ≥ 20 mg/d for persons weighing > 10 kg) for ≥ 14 consecutive days within 14 days prior to or 30 days after each vaccination during conduct of the study.

      **Note**: Topical, ophthalmic and inhaled steroids are permitted.

15. *Has received other licensed non-live vaccines within the 14 days before receipt of first dose of study vaccine.

16. *Has received a licensed live virus vaccine within the 28 days before receipt of first dose of study vaccine.

17. Has received a blood transfusion or blood products, including immunoglobulins before receipt of first dose of study vaccine.

### Prior/Concurrent Clinical Study Experience

18. Has participated in another clinical study of an investigational product before the beginning or anytime during the duration of the current clinical study. Participants enrolled in observational studies may be included; these will be reviewed on a case by-case basis for approval by the Sponsor.

### Other Exclusions

19. Has any other reason that, in the opinion of the investigator, may interfere with the evaluation required by the study. (Refer to the Vaccination Guideline in Japan). Reasons may include, but are not limited to, being unable to keep appointments or planning to relocate during the study.

20. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

**For item with an asterisk (*), if the participant meets these exclusion criteria, Visit 1 may be rescheduled for a time when these criteria are not met.**

## 5.3 Lifestyle Considerations

No lifestyle restrictions are required.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

## 5.5 Participant Replacement Strategy

A participant who discontinues from study vaccination OR withdraws from the study will not be replaced.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (V114, PCV13 and DTaP-IPV) will be packaged to support enrollment . Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

## 6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

| Arm Name | Arm Type | Intervention Name | Type | Dose Formulation | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Vaccination Regimen | Use | IMP/ NIMP | Sourcing |
|---|---|---|---|---|---|---|---|---|---|---|---|
| V114-SC | Experimental | V114 | Biological /Vaccine | Sterile Suspension | Refer to IB | 0.5 mL | SC | Single Dose at Visit 1, 2, 3 and 5 | Experimental | IMP | Cenral |
| V114- IM | Experimental | V114 | Biological /Vaccine | Sterile Suspension | Refer to IB | 0.5 mL | IM | Single Dose at Visit 1, 2, 3 and 5 | Experimental | IMP | Cenral |
| PCV13-SC | Active Comparator | PCV13* | Biological /Vaccine | Sterile Suspension | Refer to product labeling | 0.5 mL | SC | Single Dose at Visit 1, 2, 3 and 5 | Experimental | IMP | Cenral |
| Concomitant Vaccine | (Not Applicable) | DTaP-IPV** | Biological /Vaccine | Sterile Suspension | Refer to product labeling | 0.5 mL | SC | Single Dose at Visit 1, 2, 3 and 5 | Concomitant | IMP | Central |

Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) are based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed

PCV13 *: Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein) DTaP-IPV **: Adsorbed Diphtheria-purified Pertussis-tetanus-inactivated polio (Sabin strain) Combined Vaccine

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

## 6.2 Preparation/Handling/Storage/Accountability

### 6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

### 6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

## 6.3 Measures to Minimize Bias: Randomization and Blinding

### 6.3.1 Intervention Assignment

Participants will be assigned randomly according to a computer-generated allocation schedule. There are 3 study intervention groups. Participants will be assigned randomly in a 1:1:1 ratio to V114-SC study vaccination group, V114-IM study vaccination group or active control group (PCV13-SC), respectively.

### 6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

### 6.3.3 Blinding

A double-blinding technique will be used. V114 and PCV13 will be prepared and/or dispensed by an unblinded pharmacist or unblinded qualified study personnel. The participant and the investigator who are involved in the clinical evaluation of the participants will remain blinded to the group assignments until end of the study.

Because the V114 and PCV13 have a different appearance, a member of the study site personnel will be unblinded for the purposes of receiving, maintaining, preparing and/or dispensing, and administering the study vaccine. Procedures for handling, preparing, and administering the unblinded vaccines are located in the Investigator Trial File Binder.

Due to differences in appearance, vaccine administration will be performed by unblinded study personnel who will have no contact with study participants other than administration of study vaccine, which includes all safety follow up procedures at each vaccination visit. Additionally, blinded site personnel and participant's parent/guardian will remain blinded such as not to be present in the same room or to be separated with a curtain when V114 and PCV13 are administered. Contact between participants and unblinded study personnel after each vaccination administration is strictly prohibited. Blinded study personnel will be responsible for all safety and immunogenicity follow-up procedures after study vaccine administration.

An unblinded Clinical Research Associate will monitor study vaccine accountability at the study site. All other Sponsor personnel or delegate(s) directly involved with the conduct of this study will remain blinded to the participant-level intervention assignment until the end of the study. See Section 8.1.11 for a description of the method of unblinding a participant during the study should such action be warranted.

## 6.4 Study Intervention Compliance

Interruptions from the protocol-specified plan for V114 or PCV13 vaccination indicated in Section 1.3 require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

## 6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study (See section 5.2 for details). If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to

continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant's legally acceptable representative.

If a medical condition requires the use of a prohibited steroid regimen, immunoglobulin, blood, or blood products during a subject's participation in this trial, one of the individuals listed on the Sponsor Contact Information page must be notified as soon as possible. Any concurrent medication or medical treatment must be recorded on the appropriate electronic case report form (eCRF). It is important to record the use of any analgesic or antipyretic use on the VRC and appropriate eCRF.

The V114/PCV13 and concomitant vaccine (DTaP-IPV) will be administered at Visit 1, 2, 3 and 5 (approximately 3, 4, 5 and 12 to 15 months of age). Subjects should not receive systemic corticosteroids (equivalent of ≥2 mg/kg total daily dose of prednisone or ≥20 mg/d for persons weighing >10 kg for ≥14 consecutive days) starting from 14 days prior to each vaccination through 30 days after each vaccination. Topical, ophthalmic and inhaled steroids are permitted.

Other nonstudy pediatric vaccines (oral or injectable) including NIP vaccine can be administered concomitantly according to the recommended schedule. If given at a study visit, nonstudy pediatric vaccines should be administrated with the study vaccine. These vaccinations should be recorded on the appropriate eCRF. To avoid any confounding results, nonstudy injectable vaccines should not be administered in the same limb as study vaccine.

During the influenza season, it is anticipated that participants 6 months of age and older may be given an influenza vaccine. Influenza vaccine should be administered either 7 days before or 15 days after the administration of the study vaccine.

Documentation of which limb was used for the administration of study vaccines and nonstudy vaccines should be recorded on the appropriate eCRF. As the trial is reporting injection-site AEs from the study vaccine, including DTaP-IPV vaccine (and not from the nonstudy pediatric vaccines), this information should also be recorded on the VRC to inform the parent/guardian of the appropriate limb to monitor for AEs related to the study vaccine.

No other investigational compound or device may be administered at any time during this study without prior approval by the Sponsor.

### 6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

## 6.6 Dose Modification (Escalation/Titration/Other)

No dose modification is allowed in this study.

## 6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

## 6.8 Clinical Supplies Disclosure

This study is blinded but supplies are provided as open label; therefore, an unblinded pharmacist or qualified study site personnel will be used to open supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the intervention allocation/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.11). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.11 for a description of the method of unblinding a participant during the study, should such action be warranted.

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified vaccinations will still continue to participate in the study as specified in Section 1.3 and Section 8.12.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.10 and Section 8.12.3.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.

- The participant's treatment assignment is unblinded by the investigator or through the emergency unblinding call center.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

For participants who are discontinued from study intervention but continue to be monitored in the study, see Section 1.3 and Section 8.12.3 for those procedures to be completed at each specified visit.

Discontinuation from study intervention is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

## 7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

## 7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

# 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

For all the participants in the Immunogenicity, approximately 3 mL of blood will be drawn at Visit 1 and approximately 5 mL of blood will be drawn at the Visit 4, 5 and 6. The maximum amount of blood collected from each participant over the duration of the study during planned study visits will not exceed 18 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Administrative and General Procedures

### 8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research.If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

#### 8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

#### 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant's legally acceptable representative, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the future biomedical research substudy. A copy of the informed consent will be given to the participant's legally acceptable representative.

### 8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study. The investigator should consult with the Sponsor's Clinical Director for any questions about participant eligibility.

If the participant meets any of the exclusion criteria with an asterisk (*), Visit 1 may be rescheduled for a time when these criteria are not met.

### 8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

### 8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee before vaccination at Visit 1. Weight at baseline, birth weight and gestational age will be recorded on the appropriate eCRF.

### 8.1.5 Prior and Concomitant Medications Review

#### 8.1.5.1 Prior Medications

The investigator or qualified designee will review and record prior vaccinations from birth and medications taken by the participant within 30 days before the first dose of study vaccine at Visit 1.

#### 8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

If a medical condition requires the use of a prohibitive steroid regimen, immunoglobulin, blood, or blood products during a participant's participation in this study, one of the individuals listed on the Sponsor Contact Information page must be notified as soon as possible. Any concurrent medication or medical treatment must be recorded on the appropriate eCRF.

It is important to record any analgesic or antipyretic use that occurs on the day of vaccination on the VRC and appropriate eCRF. Concomitant medications taken after Visit 1 and nonstudy pediatric vaccines received since Visit 1 will be recorded with the VRC as specified in Section 8.3.3.

Nonstudy pediatric vaccines administered during the study should be recorded on the appropriate eCRF. Injectable vaccines should not be administered in the same limb as study vaccine. Documentation of which limb was used for the administration of study vaccine must be recorded on the VRC (Section 8.3.3) and appropriate eCRF.

### 8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.12.1.

### 8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The treatment/randomization number identifies the participant for all procedures occurring after allocation/randomization. Once a randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 randomization number.

### 8.1.8 Study Intervention Administration

Unblinded study personnel not otherwise involved in the conduct of the study will prepare and administer the study vaccine. Study vaccines should be administered by appropriately qualified members of the study personnel (physician or nurse). Procedures for handling, preparing, and administering the unblinded vaccines are provided in the Investigator Trial File Binder. Unblinded study personnel should follow the preparation and administration instructions for PCV13 as specified in the product label.

V114 and PCV13 should be removed from the refrigerator no more than 1 hour before vaccination. The time of removal and time of vaccination should be documented in the participant's chart.

V114 is provided as a vial. Prior to administration of study vaccine, the unblinded study personnel should use rapid, horizontal hand-shaking for up to 5 seconds while holding the vial in between the thumb and index finger to obtain a homogenous white suspension. This

action should be repeated, as necessary. If appearance is otherwise, the vaccine should not be administered. The vaccine should not be used if the vaccine cannot be resuspended.

A 0.5-mL vaccination dose of V114/PCV13 will be administered to healthy infants at Visit 1, 2, 3 and 5 (approximately 3, 4, 5, and 12 to 15 months of age). PCV13 will be supplied as a pre-filled syringe. V114/PCV13 is recommended to be administered in the right thigh. If an abnormality (i.e., rash) is observed at the site where the previous dose of the vaccine was administered, it is permissible to use another limb to administer the following dose of the study vaccine. Adequate treatment provision, including epinephrine and equipment for maintaining an airway, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Simons FE., et al 2011].

Concomitant study vaccine (DTaP-IPV) should be administered subcutaneously on the same time as V114/PCV13. DTaP-IPV is recommended to be administered in the left thigh, and nonstudy pediatric vaccines (oral and injectable) administrated concomitantly should be given with study vaccines. To avoid any confounding results, nonstudy injectable vaccines should not be administered in the same limb as study vaccine.

Unblinded study personnel should not have contact with participants for any study-related procedures/assessments other than administration of vaccines, which includes all safety follow-up procedures at vaccination visit. All clinical assessments will be conducted by blinded personnel, and the participant or participant's parent/guardian will remain blinded to the group assignments until the end of study. Vaccination information, such as Component Identification Number and date of vaccination, location of administration must be recorded on the appropriate eCRF as per the Data Entry Guidelines.

#### 8.1.8.1 Timing of Dose Administration

The study vaccine will be administered as indicated in Section 1.3. All participants will be observed for 30 minutes following each vaccination for any immediate reactions. This observation must be performed by blinded site personnel for V114 or PCV13 (Section 1.3 and Section 6.3.3).

Participants must be afebrile (axillary temperature <37.5°C) for at least 72 hours prior to vaccination.

Blood samples for participants in the study must be collected before study vaccination.

### 8.1.9 Vaccination Report Card

The investigator or delegate will train the participant's parent/guardian in the use of the VRC as indicated in Section 1.3.

Body temperatures, injection-site reactions, vaccine-specific complaints, other complaints or illnesses, and concomitant medications or nonstudy vaccinations will be recorded on the VRC as described in Section 1.3 and Section 8.3.3. The investigator or delegate will review

the data captured on the VRC with the participant's parent/guardian as indicated in Section 1.3.

For the AEs outlined above, the investigator will use the information provided by the participant's parent/guardian both on the VRC, and verbally at the time of VRC review, to apply the appropriate assessment of intensity as described in Appendix 3.

### 8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the protocol-specified vaccinations should be encouraged to continue to be followed for all remaining study visits as outlined in the 1.3 and Section 8.12.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study visit (Visit 6) should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

#### 8.1.10.1 Withdrawal From Future Biomedical Research

Consent for future biomedical research may be withdrawn by the participant's legally acceptable representative. Consent may be withdrawn by the legally acceptable representative at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant's legally acceptable representative of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

### 8.1.11 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding that is part of the study design has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

### 8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

## 8.2 Immunogenicity Assessments

Sera from participants will be used to measure vaccine-induced anti-PnPs serotype-specific IgG for all the 15 serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F) contained in V114 using the PnECL v2.0 assay. DTaP-IPV antibody titers will be measured by neutralization assay (diphtheria toxin and poliovirus 1/2/3), particle agglutination assay (tetanus toxin) and enzyme-linked immunosorbent assay (ELISA) methodology (pertussis PT and pertussis FHA).

Blood collection, storage and shipment instructions for serum samples will be provided in the operations/laboratory manual.

The Sponsor has developed and optimized a multiplex, electrochemiluminescence (ECL)-based detection method for the quantitation of IgG serotype-specific antibodies to the 15 PnPs serotypes contained in V114. The PnECL v2.0 assay is based on the Meso-Scale Discovery technology, which employs disposable multi-spot microtiter plates. The benefits of the ECL multiplex technology over the prior ELISA methodology include speed, equivalent or better sensitivity, increased dynamic range, the ability to multiplex, and reduction in required serum sample and reagent volumes. The measurement of immune responses to the 15 serotypes included in V114 is performed using an assay format consisting of 2 groups of 7 and 8 serotypes each. The PnECL v2.0 assay for all 15 serotypes has undergone validation. The validation study evaluated various performance parameters of the assay including precision, ruggedness, relative accuracy, dilutional linearity, selectivity, and specificity. The validation results were evaluated against pre-specified acceptance criteria for each of the parameters.

The WHO Expert Committee on Biological Standardization has recommended that in-house assays used in immunogenicity studies designed to evaluate protection against IPD be bridged to the WHO reference assay in order to maintain the link between immune responses to vaccination and the clinical demonstration of protective efficacy against IPD conferred by the 7 conjugated polysaccharides in Prevnar™. In 2012 and 2014, the Sponsor formally bridged the original PnECL assay to the WHO IgG ELISA in order to determine the PnECL threshold values that correspond to 0.35 µg/mL in the WHO ELISA for each of the 7 Prevnar™ serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) and for each of the additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A) in Prevnar 13™.

A confirmatory study was performed to formally bridge the optimized PnECL assay (v2.0) to the WHO reference ELISA, and to assess the PnECL threshold values that correspond to 0.35 µg/mL measured using the WHO ELISA for each of the serotypes in V114, including the PCV13 serotypes and serotypes 22F and 33F, which were not previously assessed. The bridging of the optimized PnECL to the WHO ELISA is complete, and the data showed good concordance between the PnECL and WHO ELISA around the 0.35 µg/mL threshold value for all 15 serotypes. It is recommended that a single PnECL threshold value of 0.35 µg/mL be applied to each of the 15 serotypes.

## 8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prevaccination to postvaccination visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 8.

Planned time points for all safety assessments are provided in the SoA.

### 8.3.1 Physical Examinations

A full physical examination will be performed at Visit 1. A targeted physical examination will be performed at subsequent vaccination visits (Visit 2, 3, and 5). Any clinically significant abnormality will be recorded on the appropriate eCRF.

The full and targeted physical examination procedures both include obtaining vital signs (heart rate, respiratory rate, and axillary temperature), auscultation of the heart and lung, and examination of the abdomen. In addition, a full physical examination will include an assessment of the head, eyes, ears, nose and throat, skin, lymph nodes, neurological system, and musculoskeletal system.

Findings related to the physical examinations should be documented in the participant's chart/source documentation.

### 8.3.2 Body Temperature Measurements

Pre-vaccination axillary temperatures will be taken by study personel as indicated in Section 1.3. Participants who have febrile illness (axillary temperature ≥37.5°C) occurring at or within 72 hours of Visits 1, 2, 3, and 5 must be rescheduled. Post-vaccination axillary temperatures must be recorded on the VRC. Temperature readings should be taken at approximately the same time each day. Use of temporal or tympanic thermometers to collect temperature for this study is prohibited.

The participant's parent/guardian will be asked to record the participant's temperature reading on the VRC from Day 1 through Day 7 following each vaccination. Temperature measurement must be recorded in the VRC if fever is suspected during Day 8 through Day 14.

### 8.3.3 Safety Assessment and Use of the VRC

All participants will be observed for 30 minutes after each vaccination for any immediate reactions. If any immediate AEs are observed during this period, the time at which the event occurred within this timeframe, as well as the event itself, any concomitant medications that were administered, and resolution of the event, must be recorded on the appropriate eCRF.

Participant's parent/guardian will use the VRC (Section 8.1.9) to document the following information:

- Axillary temperatures measured Day 1 (day of vaccination) through Day 7 following each vaccination; Day 8 through Day 14 following each vaccination if fever is suspected

- Solicited injection-site AEs (swelling, redness, pain or tenderness, and hard lump) Day 1 through Day 14 postvaccination

- Solicited systemic AEs (irritability, drowsiness, appetite lost, and hives or welts) Day 1 through Day 14 postvaccination

- Any other unsolicited injection-site or systemic AEs Day 1 through Day 14 postvaccination

- The limb that was used for the administration of study vaccine

  (**Note**: The study will report injection-site AEs from V114/PCV13 and DTaP-IPV [and not from nonstudy concomitant injectable vaccines]; the locations of study vaccines administration can be used by the participant's parent/guardian to monitor the appropriate limb for injection-site AEs related to V114/PCV13 and DTaP-IPV)

- Concomitant medications and nonstudy vaccinations Day 1 through Day 14 postvaccination

### 8.3.4 Clinical Safety Laboratory Assessments

There are no laboratory safety evaluations required by the protocol.

## 8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

### 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

All AEs, SAEs, and other reportable safety events must be reported by the investigator from the day of allocation/randomization to the first vaccination and from the day of each vaccination through 14 days postvaccination. SAEs must also be reported throughout the duration of the individual's participation in the study, regardless of whether or not related to the Sponsor's product.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is either:

1. A death that occurs prior to the participant completing the study.

OR

2. An SAE that is considered by an investigator who is a qualified physician to be vaccine-related.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

| **Type of Event** | **Reporting Time Period: Consent to Randomization/ Allocation** | **Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period** | **Reporting Time Period: After the Protocol-specified Follow-up Period** | **Time Frame to Report Event and Follow-up Information to Sponsor:** |
|---|---|---|---|---|
| Nonserious Adverse Event (NSAE) | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- participant is receiving placebo run-in or other run-in treatment | Report all | Not required | Per data entry guidelines |
| Serious Adverse Event (SAE) | Report if:<br>- due to protocol-specified intervention<br>- causes exclusion<br>- participant is receiving placebo run-in or other run-in treatment | Report all | Report if:<br>- drug/vaccine related.<br>- any death until participant completion of study<br>(Follow ongoing to outcome) | Within 24 hours of learning of event |
| Pregnancy/Lactation Exposure | Not applicable since participants are infants. | | | Not applicable |
| Event of Clinical Interest | There are no ECIs for this study. | | | Not applicable |
| Cancer | Report if:<br>- due to intervention<br>- causes exclusion | Report all | Not required | Within 5 calendar days of learning of event |
| Overdose | Report if:<br>- receiving placebo run-in or other run-in medication | Report all | Not required | Within 5 calendar days of learning of event |

### 8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

### 8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

### 8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply wth country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

### 8.4.5 Pregnancy and Exposure During Breastfeeding

Information in this section is not applicable since participants are infants.

### 8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

This is not applicable to this study.

### 8.4.7 Events of Clinical Interest (ECIs)

There are no events of clinical interest in this study.

## 8.5 Treatment of Overdose

In this study, an overdose is the administration of more than 1 dose of any individual study vaccine in any 24-hour period.

No specific information is available on the treatment of overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

All reports of overdose must be reported by the investigator within 5 calendar days to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the eCRF data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

## 8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

## 8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

## 8.8 Future Biomedical Research Sample Collection

If the participant's legally acceptable representative signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Buccal swab DNA for future research
- Leftover study serum for IgG at the central laboratory stored for future research after aliquoting samples for completion of immunogenicity

## 8.9 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

## 8.10 Biomarkers

Biomarkers are not evaluated in this study.

## 8.11 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study

## 8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

### 8.12.1 Screening

Screening procedures will be conducted at Visit 1 as outlined in Section 1.3.

### 8.12.2 Treatment Period/Vaccination Visit

Requirements during the treatment period/vaccination visit are outlined in Section 1.3.

If the participant develops a new clinical condition during the study that makes him/her ineligible for the study, the investigator should discuss with the Sponsor Clinical Director as soon as possible. The decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant's legally acceptable representative.

### 8.12.3 Discontinued Participants Continuing to be Monitored in the Study

A participant may discontinue from study intervention (including receipt of V114 or PCV13) but continue to participate in protocol-specified, AE-monitoring activities as outlined in Section 1.3, as long as the participant's legally acceptable representative does not withdraw consent. Blood draws for immunogenicity testing in the study could occur if agreed to by the participant's legally acceptable representative at the discretion of the investigator.

## 9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

### 9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 - 9.12.

| | |
|---|---|
| Trial Design Overview | A Phase I, Double-Blind, Randomized, Multicenter Trial of the Safety, Tolerability, and Immunogenicity of V114 in Healthy Japanese Infants |
| Treatment Assignment | This is a double-blind trial with three vaccination groups. Participants will be randomized to V114-SC, V114-IM, and PCV13-SC in a 1:1:1 ratio. |
| Analysis Populations | Safety<br>All Participants as Treated (APaT)<br>Immunogenicity<br>Primary: Per-protocol (PP) |
| Primary Endpoints | 1. Solicited injection-site AEs (redness, swelling, hard lump, pain/tenderness) from Day 1 through Day 14 postvaccination<br>2. Solicited systemic AEs (irritability, drowsiness, hives/welts, appetite loss) from Day 1 through Day 14 postvaccination<br>3. Vaccine-related SAEs from Day 1 through 1 month PD4 |

| | |
|---|---|
| Secondary Endpoints | The following endpoints at 1 month PD3:<br>1. Anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) for the 15 serotypes contained in V114<br>2. IgG GMCs for the 15 serotypes contained in V114<br>3. Proportion of participants meeting threshold values for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA as well as polio virus types 1, 2 and 3. |
| Statistical Methods for Key Immunogenicity Analyses | The proportion of participants with IgG concentrations ≥0.35 µg/mL at 1 month PD3 for the 15 serotypes contained in V114 will be summarized by vaccination group. Within-group 95% CIs will be calculated based on the method of Clopper and Pearson. The between-group differences, along with the corresponding 95% CIs based on the method of Miettinen and Nurminen [Miettinen O., et al 1985], will be calculated. The proportion of participants meeting threshold values at 1 month PD3 for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA as well as polio virus types 1, 2 and 3 will be analyzed in the same fashion.<br>The IgG concentrations at 1 month PD3 will be natural log transformed and analyzed using an analysis of variance (ANOVA) model with a single factor for vaccination group. The within-group means and the between-group mean differences, along with the corresponding 95% CIs, will be estimated using this model. The point estimates as well as the lower and upper limits of the 95% CIs will be exponentiated to obtain the estimates on the original scale for IgG GMCs by vaccination group and IgG GMC ratios. |
| Statistical Methods for Key Safety Analyses | The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed.<br>Tier 1 safety endpoints include solicited injection-site AEs and solicited systemic AEs during Day 1 to Day 14 postvaccination that are specifically prompted for on the VRC. Endpoints not defined as Tier 1 will be classified as belonging to "Tier 2" or "Tier 3". Tier 2 endpoints include AE summary measures (any AE, any vaccine-related AE, any SAE, any vaccine-related SAE, discontinuation of study vaccine due to an AE), AEs [specific terms as well as system organ classes (SOCs)] that occur in at least 4 subjects in any vaccination group, and axillary temperatures (≥37.5 °C, ≥38.0 °C, ≥39.0 °C, ≥40.0 °C) collected from Day 1 through Day 7.<br>p-Values (for Tier 1 endpoints) and 95% CIs (for Tier 1 and Tier 2 endpoints) will be provided for between-group differences in the percentage of participants with events. These analyses will be performed using the Miettinen and Nurminen method. |
| Interim Analysis | An interim analysis will be performed after all participants continuing on the trial have completed the study visit at 1 month PD3 and the data (safety and immunogenicity) up to that point have become available. Group summaries of the results will be reviewed; however, the study team will remain blinded at the subject level. Only designated unblinded Sponsor personnel will review the safety data at the subject level, and will be responsible for communicating in a blinded manner to the blinded study team. The information noted above will be used to make scientific decisions regarding future studies. The conduct of this trial will not be altered by the interim analysis. |
| Multiplicity | Multiplicity adjustment is not planned. |
| Sample Size and Power | A total of 120 participants will be equally randomized, with 40 participants in each of the three vaccination groups. If the true incidence of a particular safety event is 4%, then there is 80% probability that the event is observed in at least one in 40 participants. |

## 9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this trial will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This trial will be conducted as a double-blind trial under in-house blinding procedures. The Sponsor personnel, except those who are specifically designated to serve as unblinded roles (see Sections 6.3.3 and 9.7), will remain blinded to the treatment assignment of individual participants until the end of the trial. Site personnel, except those who are specifically designated to serve as unblinded roles (see Section 6.3.3), as well as participants and their parents/legal guardians, will also remain blinded until the end of the trial.

The Clinical Biostatistics department will generate the randomized allocation schedule for trial treatment assignment. Randomization will be implemented using interactive response technology (IRT) or its equivalent.

The planned interim analysis is described in Section 9.7. The results of the interim analysis will not be shared with the investigators prior to the completion of the trial. Subject-level unblinding will be restricted to the unblinded statistician and unblinded statistical programmer performing the interim analysis, as well as designated unblinded Sponsor personnel who will review safety data at the subject level. Group summaries will be reviewed by the Sponsor's trial team in order to make scientific decisions for future studies.

## 9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

## 9.4 Analysis Endpoints

Immunogenicity and safety endpoints are listed below.

### 9.4.1 Immunogenicity Endpoints

The key immunogenicity endpoints include the following, in recipients of V114-SC, V114-IM and PCV13-SC:

(1) Anti-PnPs serotype-specific IgG response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL measured by the PnECL assay) at 1 month PD3 for the 15 serotypes contained in V114.

(2) Anti-PnPs serotype-specific IgG GMCs for the 15 serotypes contained in V114, based on the serotype-specific IgG responses as measured by the PnECL assay at 1 month PD3.

(3) The proportion of participants meeting threshold values at 1 month PD3 for diphtheria toxin (≥0.1 IU/mL), tetanus toxin (≥0.01 IU/mL), pertussis toxin (≥10 EU/mL), pertussis FHA (≥10 EU/mL) as well as polio virus types 1 [neutralizing antibody titers (NA) ≥1:8], 2 (NA ≥1:8) and 3 (NA ≥1:8).

The same measures at pre Dose 4 and 1 month PD4, as well as GMTs of DTaP-IPV at 1 month PD3, pre Dose 4 and 1 month PD4 will also be analyzed.

### 9.4.2 Safety Endpoints

Refer to Section 4.2.1.2 for the description of the safety measurements in this trial.

## 9.5 Analysis Populations

### 9.5.1 Immunogenicity Analysis Populations

The PP population will serve as the primary population for the analysis of immunogenicity data in this trial. The PP population consists of those participants who are not considered protocol violators.

Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses (serotype-specific IgG and DTaP-IPV at 1 month PD3, pre-dose 4 and 1 month PD4) include:

- Failure to complete vaccination of V114 or PCV13 at Doses 1 through 3 with correct clinical material and route of administration as per the randomization schedule and according to the protocol-specified visit window (refer to Section 1.3).

- Receipt of prohibited medication or prohibited vaccine prior to study vaccination at Dose 1, 2 or 3

Additional potential deviations that may result in the exclusion of a participant from the PP population for specific immunogenicity analyses (depending on the time point or endpoint for analysis) include:

- Failure to receive V114 or PCV13 at Dose 4 with correct clinical material and route of administration as per the randomization schedule and according to the protocol-specified visit window: this will result in the exclusion from all PP analyses (serotype-specific IgG and DTaP-IPV) at 1 month PD4.

- Failure to complete vaccination of DTaP-IPV at Doses 1 through 3 according to the protocol-specified visit window: this will result in the exclusion from the PP analysis of DTaP-IPV at all timepoints.

- Failure to receive DTaP-IPV at Dose 4 according to the protocol-specified visit window: this will result in the exclusion from PP analysis of DTaP-IPV at 1 month PD4.

- Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection: the impact on the analysis of immunogenicity data will be assessed on a case-by-case basis.

- Collection of blood sample at the time point for the analysis outside of the pre-specified window, or lack of valid serology results: this will result in the exclusion from the PP analysis for particular timepoint(s) and/or endpoint(s) whose valid results are not available.

The final determination on protocol violations for 1 month PD3 analysis will be made prior to the database lock at 1 month PD3 for the interim analysis and will be documented in a separate memo. Protocol violators at Pre-dose 4 and 1 month PD4 will be identified prior to the final database lock at 1 month PD4.

The FAS population will also be used for supplementary analysis of the key immunogenicity endpoints. The FAS population consists of all randomized participants who received at least one vaccination and have at least one serology result. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data.

### 9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this trial. The APaT population consists of all randomized participants who received at least one dose of trial vaccine. Participants will be included in the group corresponding to the clinical material and route of administration they actually received for the analysis of safety data using the APaT population. For most participants this will be the group to which they are randomized. Participants who receive incorrect clinical material or whose route of administration is incorrect will be included in the group as outlined below:

- Participants who receive the same clinical material (V114 or PCV13) with the same route of administration throughout the trial will be considered belonging to the group corresponding to the clinical material and route of administration.

- Participants whose clinical materials (V114 and PCV13) and/or route of administration are partially different among the vaccinations will be summarized separately from any of the 3 vaccination groups.

- Incorrect route of administration for DTaP-IPV will not alter the vaccination group for safety analysis; the group will be determined based on the clinical material and route of administration for V114 or PCV13 only.

## 9.6 Statistical Methods

The results from all possible pairwise comparisons (V114-SC vs. PCV13-SC, V114-IM vs. PCV13-SC, V114-SC vs. V114-IM) will be presented for those analyses which involve calculations of between-group differences.

### 9.6.1 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the secondary objectives. Methods related to the exploratory objectives will be described in the sSAP.

The immunogenicity analyses will be conducted for each serotype separately.

The proportion of participants with IgG concentrations ≥0.35 µg/mL at 1 month PD3 will be summarized by vaccination group. Within-group 95% CIs will be calculated based on the method of Clopper and Pearson. The between-group differences, along with the corresponding 95% CIs based on the method of Miettinen and Nurminen, will be calculated. The proportion of participants meeting threshold values at 1 month PD3 for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA as well as polio virus types 1, 2 and 3 will be analyzed in the same fashion.

The IgG concentrations at 1 month PD3 will be natural log transformed and analyzed using an ANOVA model with a factor for vaccination group. The within-group means and the between-group mean differences, along with the corresponding 95% CIs, will be estimated using this model. The point estimates as well as the lower and upper limits of the 95% CIs will be exponentiated to obtain the estimates on the original scale for IgG GMCs by vaccination group and IgG GMC ratios.

Table 4 summarizes key immunogenicity analyses.

Table 4 Analysis Strategy for Key Immunogenicity Variables

| Endpoint / Variable (Description, Time Point) | Statistical Method[†] | Analysis Population | Missing Data Approach |
|---|---|---|---|
| Secondary objective #1 | | | |
| Proportion of participants with serotype-specific IgG ≥0.35 µg/mL at 1 month PD 3 | Miettinen and Nurminen | PP (Primary) FAS (Supportive) | Missing data will not be imputed |
| Secondary objective #2 | | | |
| Serotype-specific IgG GMCs at 1 month PD3 | ANOVA[‡] | PP (Primary) FAS (Supportive) | Missing data will not be imputed |
| Secondary objective #3 | | | |
| Proportion of participants meeting threshold values for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA as well as polio virus types 1, 2 and 3 at 1 month PD3 | Miettinen and Nurminen | PP (Primary) FAS (Supportive) | Missing data will not be imputed |

[†] Statistical models are described in further detail below:
[‡] ANOVA model with natural log-transformed antibody responses as response variable and vaccination group as a single factor
IgG = immunoglobulin G, PD = post-dose, GMC = geometric mean concentration, PP = per-protocol, FAS = full analysis set, ANOVA = analysis of variance, FHA = filamentous hemagglutinin

### 9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and body temperature. Analysis will be performed at each dose and across all doses, as outlined below.

The analysis of safety results will follow a tiered approach (Table 5). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as SOCs) are either pre-specified as “Tier 1” endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of participants with events.

Tier 1 events

AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance (at $\alpha$=0.05, two-sided) with p-values and 95% CIs to be provided for between-group differences in the proportion of participants with events. These analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method. For this protocol, Tier 1 safety endpoints include solicited injection-site AEs (redness, swelling, hard lump, pain/tenderness) and solicited systemic AEs (irritability, drowsiness, hives/welts, appetite loss) during Day 1 to Day 14 postvaccination that are specifically prompted for on the VRC.

Tier 2 events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events, also via the Miettinen and Nurminen method.

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs.

In addition to individual events that occur in 4 or more participants in any vaccination group, AE summary measures (any AE, any vaccine-related AE, any SAE, any vaccine-related SAE, discontinuation of study vaccine due to an AE), and axillary temperatures (≥37.5 °C, ≥38.0 °C, ≥39.0 °C, ≥40.0 °C) collected from Day 1 through Day 7, will also be treated as Tier 2 events. For the purpose of the analysis of safety data in this study, an AE will be considered related to study vaccine if it is considered related to V114/PCV13 or DTaP-IPV.

Tier 3 events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group will be provided for Tier 3 safety parameters.

Table 5 Analysis Strategy for Safety Parameters

| Safety Tier | Safety Endpoints | p-Value | 95% CI | Descriptive statistics |
|---|---|---|---|---|
| Tier 1 | Injection-site redness (Days 1 to 14)<br>Injection-site swelling (Days 1 to 14)<br>Injection-site hard lump (Days 1 to 14)<br>Injection-site pain/tenderness (Days 1 to 14)<br>Irritability (Days 1 to 14)<br>Drowsiness (Days 1 to 14)<br>Hives/welts (Days 1 to 14)<br>Appetite loss (Days 1 to 14) | X | X | X |
| Tier 2 | Any AE<br>Any vaccine-related AE<br>Any SAE<br>Any vaccine-related SAE<br>Discontinuation of study vaccine due to an AE<br>Specific AEs or SOCs† (incidence ≥4 participants in any vaccination group)<br>Axillary temperature (Days 1 to 7) | | X | X |
| Tier 3 | Specific AEs or SOCs† (incidence <4 participants in all vaccination groups) | | | X |

† Includes only those endpoints not pre-specified as Tier 1 or Tier 2.
X = Results will be provided.

### 9.6.3 Summaries of Demographics and Baseline Characteristics

The comparability of the vaccination groups for each relevant demographic and baseline characteristic will be assessed by the use of summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects randomized and vaccinated, and the reasons for discontinuation, will be displayed by group. Demographic variables, prior and concomitant therapies and vaccines will be summarized by group.

## 9.7 Interim Analyses

An interim analysis will be performed after all participants continuing on the trial have completed the study visit at 1 month PD3 and the data (safety and immunogenicity) up to that point have become available. An unblinded statistician and a statistical programmer who are otherwise not involved in the trial or the project will have access to the treatment assignment of individual participants to analyze the data. The project team will review group level summary results but will not be unblinded at the subject level. Designated unblinded Sponsor personnel will review subject level safety data and communicate their recommendation regarding the future study to the project team in a manner that maintains subject level blinding for blinded Sponsor personnel. The information noted above will be used to make scientific decisions regarding the future study. The results of the interim analysis will not be

shared with the investigators until the end of the trial. The conduct of this trial will not be altered by the interim analysis.

## 9.8 Multiplicity

Multiplicity adjustment is not planned.

## 9.9 Sample Size and Power Calculations

This is an estimation study. A total of 120 participants will be equally randomized, with 40 participants in each of the three vaccination groups (V114-SC, V114-IM and PCV13-SC).

Safety

If the true incidence of a particular safety event is 4%, then there is 80% probability that the event is observed in at least one in 40 participants. Detectable differences with 80% power with respect to the percent incidence of a particular safety event are summarized in Table 6 [N=40 / arm, $\alpha$=0.05 (two-sided)].

Table 6 Detectable Difference in the Percent Incidence of a Safety Event [N=40 / arm, $\alpha$=0.05 (two-sided)]

| True % incidence | | Detectable difference with 80% power |
|---|---|---|
| Group 1 | Group 2[†] | |
| 2.5% | 20.3% | 17.8% |
| 5.0% | 26.2% | 21.2% |
| 10.0% | 35.2% | 25.2% |
| 20.0% | 49.3% | 29.3% |
| 40.0% | 70.1% | 30.1% |

[†] Corresponding to the detectable difference with 80% power.

Immunogenicity at 1 month PD3 (proportion of participants achieving threshold)

It is expected that 36 participants per arm will be included in the PP population at 1 month PD3.

The between-group differences and corresponding 95% CIs for the proportion of participants achieving the threshold value for the IgG of a particular pneumococcal serotype or a component of DTaP-IPV (diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA, or polio virus types 1, 2 or 3) will be as follows, depending on the numbers of participants achieving the threshold value in the two groups.

Table 7 Between-group Difference Estimates in the Proportion of Participants Achieving Threshold Value for Immunogenicity Measurements (N=36 / arm)

| Number of participants achieving threshold value | | Proportion of participants achieving threshold value | | Difference in proportion Group 1 – Group 2 Estimate (95% CI) |
|---|---|---|---|---|
| Group 1 | Group 2 | Group 1 | Group 2 | |
| 31 | 31 | 86.1% | 86.1% | 0.0% (-17.2%, 17.2%) |
| 33 | | 91.7% | | 5.6% (-10.2%, 21.9%) |
| 35 | | 97.2% | | 11.1% (-2.2%, 26.5%) |
| 31 | 33 | 86.1% | 91.7% | -5.6% (-21.9%, 10.2%) |
| 33 | | 91.7% | | 0.0% (-14.9%, 14.9%) |
| 35 | | 97.2% | | 5.6% (-7.0%, 19.6%) |
| 31 | 35 | 86.1% | 97.2% | -11.1% (-26.5%, 2.2%) |
| 33 | | 91.7% | | -5.6% (-19.6%, 7.0%) |
| 35 | | 97.2% | | 0.0% (-11.9%, 11.9%) |

## 9.10 Subgroup Analyses

No subgroup analysis is planned.

## 9.11 Compliance (Medication Adherence)

The number and proportion of randomized participants receiving each vaccination will be summarized

## 9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered V114 or PCV13 and the number and proportion of randomized participants administered DTaP-IPV at each schedule.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### 10.1.1 Code of Conduct for Clinical Trials

**Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)**

**Code of Conduct for Interventional Clinical Trials**

**I. Introduction**

**A. Purpose**

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

**B. Scope**

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

**II. Scientific Issues**

**A. Trial Conduct**

**1. Trial Design**

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

**2. Site Selection**

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

**3. Site Monitoring/Scientific Integrity**

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

**B. Publication and Authorship**

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

## III. Participant Protection

### A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

### B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

### C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

### D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

## IV. Financial Considerations

### A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

**B. Clinical Research Funding**

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

**C. Funding for Travel and Other Requests**

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

**V. Investigator Commitment**

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

### 10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

### 10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

### 10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

### 10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

### 10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

## 10.1.4 Committees Structure

### 10.1.4.1 Internal Safety Data Assessment

Internal safety data assessment will be conducted at the interim analysis in this study. The assessment will be conducted by the members of Sponsor senior management, none of whom are directly associated with the conduct of the study. The member of internal safety data assessment will review the interim safety data that are unblinded at the subject level (Section 9.7). The information noted above will be used to make scientific decisions regarding the subsequent phases of V114 clinical development in Japanese pediatric. The results of the interim analysis will not be shared with the investigators and the project team until the end of the trial.

Specific details regarding responsibilities for internal safety data assessment will be described in separate internal procedures manual.

### 10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

### 10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

### 10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

### 10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

### 10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

### 10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

## 10.2 Appendix 2: Clinical Laboratory Tests

Not applicable.

## 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

### 10.3.1 Definition of AE

**AE definition**

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

**Events meeting the AE definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

**Events NOT meeting the AE definition**

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

### 10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

**An SAE is defined as any untoward medical occurrence that, at any dose:**

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 10.3.3 Additional Events Reported

**Additional events that require reporting**

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer

- Is associated with an overdose

### 10.3.4 Recording AE and SAE

**AE and SAE recording**

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of intensity**

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

  The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

- Injection site redness or swelling from the day of vaccination through Day 14 postvaccination will be evaluated by maximum size.

**Assessment of causality**

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialled document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

    - **Exposure**: Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?

    - **Time Course**: Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a vaccine-induced effect?

    - **Likely Cause**: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

    - **Rechallenge**: Was the participant re-exposed to the Sponsor's product in the study?

        - If yes, did the AE recur or worsen?

        - If yes, this is a positive rechallenge.

        - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose vaccine study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

**Follow-up of AE and SAE**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

### 10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

**AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool**

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

## SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

## 10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

## 10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Not applicable.

## 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

### 1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

### 2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

### 3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research substudy

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

## 4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

## 5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this substudy. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

## 6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

## 7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

## 8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

## 9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

## 10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

## 11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

## 12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@merck.com.

## 13. References

**1.** National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

**2.** International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

**3.** Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

**4.** Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

## 10.7 Appendix 7: Country-specific Requirements

Not applicable.

## 10.8 Appendix 8: Abbreviations

| Abbreviation | Expanded Term |
|---|---|
| AE | adverse event |
| APaT | all participants as treated |
| ANOVA | analysis of variance |
| CSR | Clinical Study Report |
| CDC | Centers for Disease Control and Prevention |
| ECG | electrocardiogram |
| ECL | electrochemiluminescence |
| eCRF | electronic Case Report Form |
| ELISA | enzyme-linked immunosorbent assay |
| EMA | European Medicines Agency |
| FAS | full analysis set |
| FDAAA | Food and Drug Administration Amendments Act |
| FBR | Future Biomedical Research |
| GCP | Good Clinical Practice |
| GMC | geometric mean concentration |
| GMT | geometric mean titer |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IgG | immunoglobulin G |
| IPD | invasive pneumococcal disease |
| IRB | Institutional Review Board |
| MSD | Merck Sharp & Dohme Corp. |
| NIP | National Immunization Program |
| PCV | pneumococcal conjugate vaccine |
| PD | pneumococcal disease |
| PD3 | post-Dose 3 |
| PD4 | post-Dose 4 |
| PnECL | pneumococcal electrochemiluminescence |
| PnPs | pneumococcal polysaccharide |
| PP | Per-protocol |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SoA | schedule of activities |
| SOC | system organ classes |
| sSAP | supplemental statistical analysis plan |
| VRC | Vaccination Report Card |
| WHO | World Health Organization |

# 11 REFERENCES

[Cherian T. 2007] Cherian T. WHO expert consultation on serotype composition of pneumococcal conjugate vaccines for use in resource-poor developing countries, 26-27 October 2006, Geneva. Vaccine. 2007;25:6557-64.

[Nakano S., et al 2016] Nakano S, Fujisawa T, Ito Y, et al. Serotypes, antimicrobial susceptibility, and molecular epidemiology of invasive and non-invasive Streptococcus pneumoniae isolates in pediatric patients after the introduction of 13-valent conjugate vaccine in a nationwide surveillance study conducted in Japan in 2012-2014. Vaccine. 2016; 34:67-76.

[Golden AR., et al 2016] Golden AR, Adam HJ, Zhanel GG, et al. Invasive Streptococcus pneumoniae in Canada, 2011–2014: Characterization of new candidate 15-valent pneumococcal conjugate vaccine serotypes 22F and 33F. Vaccine. 2016; 34:2527-30.

[Pilishvili T., et al 2010] Pilishvili T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis. 2010; 201:32-41.

[Robinson KA., et al, 2001] Robinson KA, Baughman W, Rothrock G, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: Opportunities for prevention in the conjugate vaccine era. JAMA. 2001; 285:1729-35.

[Centers for Disease Control and Prevention 1997] Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCS) Report Emerging Infections Program Network Streptococcus pneumoniae, 1997

[Centers for Disease Control and Prevention 2016] Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCS) Report Emerging Infections Program Network Streptococcus pneumoniae, 2016

[Chiba N., et al 2014] Chiba N, Morozumi M, Shouji M, et al. Changes in Capsule and Drug Resistance of Pneumococci after Introduction of PCV7, Japan, 2010–2013. Emerg Infect Dis. 2014; 20:1132-9.

[Japan Pediatric Society 2014] Japan Pediatric Society. Request for guideline of administration method of vaccination. 2014Jun14 [in Japanese]

[World Health Organization 2017-1] World Health Organization. Weekly epidemiological record (Diphtheria vaccine: WHO position paper – August 2017). 2017, 92, 417-36.

[World Health Organization 2017-2] World Health Organization. Weekly epidemiological record (Tetanus vaccines: WHO position paper – February 2017). 2017, 92, 53-76.

[Ministry of Health, Labor and Welfare., et al 2013] Ministry of Health, Labor and Welfare, Infectious disease Surveillance Center. Infectious disease epidemic prediction research report. 2013.

https://www.niid.go.jp/niid/images/epi/yosoku/AnnReport/2013-all.pdf

[Plotkin PA. 2010] Plotkin PA. Correlates of Protection Induced by Vaccination. Clin Vaccine Immunol. 2010; 17:1055-65.

[Kato T. 1990] Kato T. DTaP. J Pediatric Practice 1990; 53:2275-81 [in Japanese]

[Simons FE., et al 2011] Simons FE, Ardusso LR, Bilò MB, et al. World Allergy Organization Guidelines for the Assessment and Management of Anaphlaxis. 2011; 2:13-37.

[Miettinen, O., et al 1985]. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985; 4:213-26.

Supplemental Statistical Analysis Plan (sSAP)

# 1 INTROCUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

# 2 SUMMARY OF CHANGES

[15-Nov-2019]
Section 3.6.1 Statistical Methods for Immunogenicity Analyses
The following analyses have been added:

- Analyses of IgG (proportion of participants ≥0.35 µg/mL and GMC) in subjects with baseline IgG <0.35 µg/mL.
- Reverse cumulative distribution curves

Appendix
Reference to the patient registration center has been removed, and the reference to the unblinded clinical scientist has been added.

# 3 ANALYTICAL AND METHODOLOGICAL DETAILS

## 3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 3.2 – 3.12.

| | |
|---|---|
| Trial Design Overview | A Phase I, Double-Blind, Randomized, Multicenter Trial of the Safety, Tolerability, and Immunogenicity of V114 in Healthy Japanese Infants |
| Treatment Assignment | This is a double-blind trial with three vaccination groups. Participants will be randomized to V114-subcutaneous (SC), V114-intramuscular (IM), and PCV13-SC in a 1:1:1 ratio. |
| Analysis Populations | Safety<br>All Participants as Treated (APaT)<br>Immunogenicity<br>Primary: Per-protocol (PP) |
| Primary Endpoints | Solicited injection-site adverse events (AEs) (redness, swelling, hard lump, pain/tenderness) from Day 1 through Day 14 postvaccination<br>Solicited systemic AEs (irritability, drowsiness, hives/welts, appetite loss) from Day 1 through Day 14 postvaccination<br>Vaccine-related serious AEs (SAEs) from Day 1 through 1 month post-Dose 4 (PD4) |
| Secondary Endpoints | The following endpoints at 1 month post-Dose 3 (PD3):<br>Anti-pneumococcal polysaccharide (PnPs) serotype-specific immunogloburin G (IgG) response rates (proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL) for the 15 serotypes contained in V114<br>IgG geometric mean concentrations (GMCs) for the 15 serotypes contained in V114<br>Proportion of participants meeting threshold values for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis filamentous hemagglutinin (FHA) as well as polio virus types 1, 2 and 3. |

| | |
|---|---|
| Statistical Methods for Key Immunogenicity Analyses | The proportion of participants with IgG concentrations ≥0.35 µg/mL at 1 month PD3 for the 15 serotypes contained in V114 will be summarized by vaccination group. Within-group 95% confidence intervals (CIs) will be calculated based on the method of Clopper and Pearson. The between-group differences, along with the corresponding 95% CIs based on the method of Miettinen and Nurminen [Miettinen O., et al 1985], will be calculated. The proportion of participants meeting threshold values at 1 month PD3 for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA as well as polio virus types 1, 2 and 3 will be analyzed in the same fashion.<br>The IgG concentrations at 1 month PD3 will be natural log transformed and analyzed using an analysis of variance (ANOVA) model with a single factor for vaccination group. The within-group means and the between-group mean differences, along with the corresponding 95% CIs, will be estimated using this model. The point estimates as well as the lower and upper limits of the 95% CIs will be exponentiated to obtain the estimates on the original scale for IgG GMCs by vaccination group and IgG GMC ratios. |
| Statistical Methods for Key Safety Analyses | The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed.<br>Tier 1 safety endpoints include solicited injection-site AEs and solicited systemic AEs during Day 1 to Day 14 postvaccination that are specifically prompted for on the vaccination report card (VRC). Endpoints not defined as Tier 1 will be classified as belonging to "Tier 2" or "Tier 3". Tier 2 endpoints include AE summary measures (any AE, any vaccine-related AE, any SAE, any vaccine-related SAE, discontinuation of study vaccine due to an AE), AEs [specific terms as well as system organ classes (SOCs)] that occur in at least 4 subjects in any vaccination group, and axillary temperatures (≥37.5 °C, ≥38.0 °C, ≥39.0 °C, ≥40.0 °C) collected from Day 1 through Day 7.<br>p-Values (for Tier 1 endpoints) and 95% CIs (for Tier 1 and Tier 2 endpoints) will be provided for between-group differences in the percentage of participants with events. These analyses will be performed using the Miettinen and Nurminen method. |
| Interim Analysis | An interim analysis will be performed after all participants continuing on the trial have completed the study visit at 1 month PD3 and the data (safety and immunogenicity) up to that point have become available. Group summaries of the results will be reviewed; however, the study team will remain blinded at the subject level. Only designated unblinded Sponsor personnel will review the safety data at the subject level, and will be responsible for communicating in a blinded manner to the blinded study team. The information noted above will be used to make scientific decisions regarding future studies. The conduct of this trial will not be altered by the interim analysis. |
| Multiplicity | Multiplicity adjustment is not planned. |
| Sample Size and Power | A total of 120 participants will be equally randomized, with 40 participants in each of the three vaccination groups. If the true incidence of a particular safety event is 4%, then there is 80% probability that the event is observed in at least one in 40 participants. |

## 3.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this trial will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This trial will be conducted as a double-blind trial under in-house blinding procedures. The Sponsor personnel, except those who are specifically designated to serve as unblinded roles (see Section 6.3.3 of the protocol, and Section 3.7), will remain blinded to the treatment assignment of individual participants until the end of the trial. Site personnel, except those who are specifically designated to serve as unblinded roles (see Section 6.3.3 of the protocol), as well as participants and their parents/legal guardians, will also remain blinded until the end of the trial.

The Clinical Biostatistics department will generate the randomized allocation schedule for trial treatment assignment. Randomization will be implemented using interactive response technology (IRT) or its equivalent.

The planned interim analysis is described in Section 3.7. The results of the interim analysis will not be shared with the investigators prior to the completion of the trial. Subject-level unblinding will be restricted to the unblinded statistician and unblinded statistical programmer performing the interim analysis, as well as designated unblinded Sponsor personnel who will review safety data at the subject level. Group summaries will be reviewed by the Sponsor's trial team in order to make scientific decisions for future studies.

## 3.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3 of the protocol.

## 3.4 Analysis Endpoints

Immunogenicity and safety endpoints are listed below.

### 3.4.1 Immunogenicity Endpoints

The key immunogenicity endpoints include the following, in recipients of V114-SC, V114-IM and PCV13-SC:

(1) Anti-PnPs serotype-specific IgG response rates [proportion of participants meeting serotype-specific IgG threshold value of ≥0.35 µg/mL measured by the pneumococcal electrochemiluminescence (PnECL) assay] at 1 month PD3 for the 15 serotypes contained in V114.

(2) Anti-PnPs serotype-specific IgG GMCs for the 15 serotypes contained in V114, based on the serotype-specific IgG responses as measured by the PnECL assay at 1 month PD3.

(3) The proportion of participants meeting threshold values at 1 month PD3 for diphtheria toxin (≥0.1 IU/mL), tetanus toxin (≥0.01 IU/mL), pertussis toxin (≥10 EU/mL), pertussis FHA (≥10 EU/mL) as well as polio virus types 1 [neutralizing antibody titers (NA) ≥1:8], 2 (NA ≥1:8) and 3 (NA ≥1:8).

The same measures at pre Dose 4 and 1 month PD4, as well as geometric mean titers (GMTs) of diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (DTaP-IPV) at 1 month PD3, pre Dose 4 and 1 month PD4 will also be analyzed.

### 3.4.2 Safety Endpoints

Refer to Section 4.2.1.2 of the protocol for the description of the safety measurements in this trial.

## 3.5 Analysis Populations

### 3.5.1 Immunogenicity Analysis Populations

The PP population will serve as the primary population for the analysis of immunogenicity data in this trial. The PP population consists of those participants who are not considered protocol violators.

Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses (serotype-specific IgG and DTaP-IPV at 1 month PD3, pre-dose 4 and 1 month PD4) include:

- Failure to complete vaccination of V114 or PCV13 at Doses 1 through 3 with correct clinical material and route of administration as per the randomization schedule and according to the protocol-specified visit window (refer to Section 1.3 of the protocol).
- Receipt of prohibited medication or prohibited vaccine prior to study vaccination at Dose 1, 2 or 3

Additional potential deviations that may result in the exclusion of a participant from the PP population for specific immunogenicity analyses (depending on the time point or endpoint for analysis) include:

- Failure to receive V114 or PCV13 at Dose 4 with correct clinical material and route of administration as per the randomization schedule and according to the protocol-specified visit window: this will result in the exclusion from all PP analyses (serotype-specific IgG and DTaP-IPV) at 1 month PD4.
- Failure to complete vaccination of DTaP-IPV at Doses 1 through 3 according to the protocol-specified visit window: this will result in the exclusion from the PP analysis of DTaP-IPV at all timepoints.
- Failure to receive DTaP-IPV at Dose 4 according to the protocol-specified visit window: this will result in the exclusion from PP analysis of DTaP-IPV at 1 month PD4.
- Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection: the impact on the analysis of immunogenicity data will be assessed on a case-by-case basis.
- Collection of blood sample at the time point for the analysis outside of the pre-specified window, or lack of valid serology results: this will result in the exclusion from the PP analysis for particular timepoint(s) and/or endpoint(s) whose valid results are not available.

The final determination on protocol violations for 1 month PD3 analysis will be made prior to the database lock at 1 month PD3 for the interim analysis and will be documented in a separate memo. Protocol violators at Pre-dose 4 and 1 month PD4 will be identified prior to the final database lock at 1 month PD4.

The full analysis set (FAS) population will also be used for supplementary analysis of the key immunogenicity endpoints. The FAS population consists of all randomized participants who received at least one vaccination and have at least one serology result. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data.

### 3.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this trial. The APaT population consists of all randomized participants who received at least one dose of trial vaccine. Participants will be included in the group corresponding to the clinical material and route of administration they actually received for the analysis of safety data using the APaT population. For most participants this will be the group to which they are randomized. Participants who receive incorrect clinical material or whose route of administration is incorrect will be included in the group as outlined below:

- Participants who receive the same clinical material (V114 or PCV13) with the same route of administration throughout the trial will be considered belonging to the group corresponding to the clinical material and route of administration.

- Participants whose clinical materials (V114 and PCV13) and/or route of administration are partially different among the vaccinations will be summarized separately from any of the 3 vaccination groups.

- Incorrect route of administration for DTaP-IPV will not alter the vaccination group for safety analysis; the group will be determined based on the clinical material and route of administration for V114 or PCV13 only.

## 3.6 Statistical Methods

The results from all possible pairwise comparisons (V114-SC vs. PCV13-SC, V114-IM vs. PCV13-SC, V114-SC vs. V114-IM) will be presented for those analyses which involve calculations of between-group differences.

### 3.6.1 Statistical Methods for Immunogenicity Analyses

The immunogenicity analyses will be conducted for each serotype separately.

The proportion of participants with IgG concentrations ≥0.35 µg/mL at 1 month PD3 will be summarized by vaccination group. Within-group 95% CIs will be calculated based on the method of Clopper and Pearson. The between-group differences, along with the corresponding 95% CIs based on the method of Miettinen and Nurminen, will be calculated. The proportion of participants meeting threshold values at 1 month PD3 for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA as well as polio virus types 1, 2 and 3 will be analyzed in the same fashion. The data (serotype-specific IgGs as well as diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA as well as polio virus types 1, 2 and 3) obtained at pre Dose 4 and 1 month PD4 will also be analysed in the same fashion.

The IgG concentrations at 1 month PD3 will be natural log transformed and analyzed using an ANOVA model with a factor for vaccination group. The within-group means and the between-group mean differences, along with the corresponding 95% CIs, will be estimated using this model. The point estimates as well as the lower and upper limits of the 95% CIs will be exponentiated to obtain the estimates on the original scale for IgG GMCs by vaccination group and IgG GMC ratios. The serotype-specific IgG concentrations obtained at pre Dose 4 and 1 month PD4, as well as the antibody titers for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA and polio virus types 1, 2 and 3 obtained at 1 month PD3, pre Dose 4 and 1 month PD4 will be analyzed in the same fashion.

The same analysis will also be peformed for IgG (proportion of participants concentrations ≥0.35 µg/mL and GMC) in subjects whose baseline IgG were <0.35 µg/mL.

For concentration or titer measurements that are smaller than the lower bound of the assay detectable range, half of the lower bound will be used for analyses.

Reverse cumulative distribution curves will be drawn by serotype and timepoint.

Table 1 summarizes immunogenicity analyses.

Table 1 Analysis Strategy for Immunogenicity Variables

| Endpoint / Variable (Description, Time Point) | Statistical Method† | Analysis Population | Missing Data Approach |
|---|---|---|---|
| Secondary objective #1 | | | |
| Proportion of participants with serotype-specific IgG ≥0.35 µg/mL at 1 month PD 3 | Miettinen and Nurminen | PP (Primary)<br>FAS (Supportive) | Missing data will not be imputed |
| Secondary objective #2 | | | |
| Serotype-specific IgG GMCs at 1 month PD3 | ANOVA‡ | PP (Primary)<br>FAS (Supportive) | Missing data will not be imputed |
| Secondary objective #3 | | | |
| Proportion of participants meeting threshold values for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA as well as polio virus types 1, 2 and 3 at 1 month PD3 | Miettinen and Nurminen | PP (Primary)<br>FAS (Supportive) | Missing data will not be imputed |
| Tertiary/Exploratory Objective #1 | | | |
| Proportion of participants with serotype-specific IgG ≥0.35 µg/mL at:<br>• Pre Dose 4<br>• 1 month PD4 | Miettinen and Nurminen | PP | Missing data will not be imputed |
| Tertiary/Exploratory Objective #2 | | | |
| Serotype-specific IgG GMCs at:<br>• Pre Dose 4<br>• 1 month PD4 | ANOVA‡ | PP | Missing data will not be imputed |
| Tertiary/Exploratory Objective #3 | | | |
| Proportion of participants meeting threshold values for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA as well as polio virus types 1, 2 and 3 at:<br>• Pre Dose 4<br>• 1 month PD4 | Miettinen and Nurminen | PP | Missing data will not be imputed |
| Tertiary/Exploratory Objective #4 | | | |
| GMTs for diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA as well as polio virus types 1, 2 and 3 at:<br>• 1 month PD3<br>• Pre Dose 4<br>• 1 month PD4 | ANOVA‡ | PP | Missing data will not be imputed |

† Statistical models are described in further detail below:
‡ ANOVA model with natural log-transformed antibody responses as response variable and vaccination group as a single factor
IgG = immunoglobulin G, PD = post-dose, GMC = geometric mean concentration, PP = per-protocol, FAS = full analysis set, ANOVA = analysis of variance, FHA = filamentous hemagglutinin

### 3.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and body temperature. Analysis will be performed at each dose and across all doses, as outlined below.

The analysis of safety results will follow a tiered approach (Table 2). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as SOCs) are either pre-specified as “Tier 1” endpoints, or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of participants with events.

Tier 1 events

AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance (at $\alpha$=0.05, two-sided) with p-values and 95% CIs to be provided for between-group differences in the proportion of participants with events. These analyses will be performed using the Miettinen and Nurminen method, an unconditional, asymptotic method. For this protocol, Tier 1 safety endpoints include solicited injection-site AEs (redness, swelling, hard lump, pain/tenderness) and solicited systemic AEs (irritability, drowsiness, hives/welts, appetite loss) during Day 1 to Day 14 postvaccination that are specifically prompted for on the VRC.

In addition, solicited injection-site AEs listed above will be summarized separately by study vaccine [V114/PCV13 (V114-SC, V114-IM, PCV13-SC), DTaP-IPV].

Tier 2 events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events, also via the Miettinen and Nurminen method.

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs.

In addition to individual events that occur in 4 or more participants in any vaccination group, AE summary measures (any AE, any vaccine-related AE, any SAE, any vaccine-related SAE, discontinuation of study vaccine due to an AE), and axillary temperatures (≥37.5 °C, ≥38.0 °C, ≥39.0 °C, ≥40.0 °C) collected from Day 1 through Day 7, will also be treated as Tier 2 events. For the purpose of the analysis of safety data in this study, an AE will be considered related to study vaccine if it is considered related to V114/PCV13 or DTaP-IPV.

Tier 3 events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group will be provided for Tier 3 safety parameters.

Table 2 Analysis Strategy for Safety Parameters

| Safety Tier | Safety Endpoints | p-Value | 95% CI | Descriptive statistics |
|---|---|---|---|---|
| Tier 1 | Injection-site redness (Days 1 to 14)<br>Injection-site swelling (Days 1 to 14)<br>Injection-site hard lump (Days 1 to 14)<br>Injection-site pain/tenderness (Days 1 to 14)<br>Irritability (Days 1 to 14)<br>Drowsiness (Days 1 to 14)<br>Hives/welts (Days 1 to 14)<br>Appetite loss (Days 1 to 14) | X | X | X |
| Tier 2 | Any AE<br>Any vaccine-related AE<br>Any SAE<br>Any vaccine-related SAE<br>Discontinuation of study vaccine due to an AE<br>Specific AEs or SOCs† (incidence ≥4 participants in any vaccination group)<br>Axillary temperature (Days 1 to 7) | | X | X |
| Tier 3 | Specific AEs or SOCs† (incidence <4 participants in all vaccination groups) | | | X |

† Includes only those endpoints not pre-specified as Tier 1 or Tier 2.
X = Results will be provided.

### 3.6.3 Summaries of Demographics and Baseline Characteristics

The comparability of the vaccination groups for each relevant demographic and baseline characteristic will be assessed by the use of summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects randomized and vaccinated, and the reasons for discontinuation, will be displayed by group. Demographic variables, prior and concomitant therapies and vaccines will be summarized by group.

The proportion of participants with serotype-specific IgG concentrations at baseline above the lower bound of the assay detectable range will be summarized by vaccination group.

## 3.7 Interim Analyses

An interim analysis will be performed after all participants continuing on the trial have completed the study visit at 1 month PD3 and the data (safety and immunogenicity) up to that point have become available. An unblinded statistician and a statistical programmer who are otherwise not involved in the trial or the project will have access to the treatment assignment of individual participants to analyze the data. The project team will review group level summary results but will not be unblinded at the subject level. (See Appendix for details.) Designated unblinded Sponsor personnel will review subject level safety data and communicate their recommendation regarding the future study to the project team in a manner that maintains subject level blinding for blinded Sponsor personnel. The information noted above will be used to make scientific decisions regarding the future study. The results of the interim analysis will not be shared with the investigators until the end of the trial. The conduct of this trial will not be altered by the interim analysis.

## 3.8 Multiplicity

Multiplicity adjustment is not planned.

## 3.9 Sample Size and Power Calculations

This is an estimation study. A total of 120 participants will be equally randomized, with 40 participants in each of the three vaccination groups (V114-SC, V114-IM and PCV13-SC).

Safety

If the true incidence of a particular safety event is 4%, then there is 80% probability that the event is observed in at least one in 40 participants. Detectable differences with 80% power with respect to the percent incidence of a particular safety event are summarized in Table 3 [N=40 / arm, $\alpha$=0.05 (two-sided)].

Table 3 Detectable Difference in the Percent Incidence of a Safety Event [N=40 / arm, $\alpha$=0.05 (two-sided)]

| True % incidence | | Detectable difference with 80% power |
|---|---|---|
| Group 1 | Group 2[†] | |
| 2.5% | 20.3% | 17.8% |
| 5.0% | 26.2% | 21.2% |
| 10.0% | 35.2% | 25.2% |
| 20.0% | 49.3% | 29.3% |
| 40.0% | 70.1% | 30.1% |

[†] Corresponding to the detectable difference with 80% power.

Immunogenicity at 1 month PD3 (proportion of participants achieving threshold)

It is expected that 36 participants per arm will be included in the PP population at 1 month PD3.

The between-group differences and corresponding 95% CIs for the proportion of participants achieving the threshold value for the IgG of a particular pneumococcal serotype or a component of DTaP-IPV (diphtheria toxin, tetanus toxin, pertussis toxin, pertussis FHA, or polio virus types 1, 2 or 3) will be as follows, depending on the numbers of participants achieving the threshold value in the two groups.

Table 4 Between-group Difference Estimates in the Proportion of Participants Achieving Threshold Value for Immunogenicity Measurements (N=36 / arm)

| **Number of participants achieving threshold value** | | **Proportion of participants achieving threshold value** | | **Difference in proportion Group 1 – Group 2 Estimate (95% CI)** |
|---|---|---|---|---|
| **Group 1** | **Group 2** | **Group 1** | **Group 2** | |
| 31 | 31 | 86.1% | 86.1% | 0.0% (-17.2%, 17.2%) |
| 33 | | 91.7% | | 5.6% (-10.2%, 21.9%) |
| 35 | | 97.2% | | 11.1% (-2.2%, 26.5%) |
| 31 | 33 | 86.1% | 91.7% | -5.6% (-21.9%, 10.2%) |
| 33 | | 91.7% | | 0.0% (-14.9%, 14.9%) |
| 35 | | 97.2% | | 5.6% (-7.0%, 19.6%) |
| 31 | 35 | 86.1% | 97.2% | -11.1% (-26.5%, 2.2%) |
| 33 | | 91.7% | | -5.6% (-19.6%, 7.0%) |
| 35 | | 97.2% | | 0.0% (-11.9%, 11.9%) |

## 3.10 Subgroup Analyses

No subgroup analysis is planned.

## 3.11 Compliance (Medication Adherence)

The number and proportion of randomized participants receiving each vaccination will be summarized

## 3.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered V114 or PCV13 and the number and proportion of randomized participants administered DTaP-IPV at each schedule.

# APPENDIX

## Access control of study data and results at interim analysis

Access to the data and results of the interim analysis will be restricted (See Section 3.7). For this purpose, access to the study folders within the computing platform for analysis and reporting will be controlled as follows.

Table 5 Access granted by folder and membership

| CPI region | TEST | PROD | PROD |
|---|---|---|---|
| Folder name (under "v114-pcv") | prot028-ia | prot028-ia | prot028-ia-summary |
| Folder use | Develop analysis programs under blinded environment | Perform interim analysis under unblinded environment | Group summary results of interim analysis results posted |
| Project team | Y | N | Y |
| Unblinded statistician / unblinded statistical programmer / unblinded clinical scientist | Y | Y | Y |
| Designated unblinded Sponsor personnel for reviewing safety data | N/A | Y | N/A |
| Y = access granted, N = access not granted, N/A = not applicable<br>CPI = computing platform integration (computing platform for analysis and reporting) | | | |

"prot028-ia" folder in the TEST region

This folder will be used by the protocol statistical programmer and the protocol statistician to develop analysis programs. This will not require any information of the actual treatment allocation of individual participants (only dummy treatment codes will be used). Prior to the database lock for the interim analysis, the study team will review the "dry run" output that are generated using the available study data up to that point in combination with the dummy treatment codes. Review of the dry run output will be conducted using the associated "-clinical" folder.

"prot028-ia" folder in the PROD region

This folder will be used by the unblinded statistician and the unblinded statistical programmer to perform interim analysis. An unblinded clinical scientist will inform the unblinded statistician and the unblinded statistical programmer of any vaccination with incorrect product and/or route of administration. Based on this information, in combination with the exclusion from analysis memo created by the blinded study team members before the database lock for the interim analysis, the unblinded statistician or the unblinded statistical programmer will flag subjects and/or datapoints within the datasets for exclusion from analysis.

All tables, listings and figures for the interim analysis will be generated in this folder by the unblinded statistician and the unblinded statistical programmer and will be provided with the designated Sponsor personnel who will review the safety data unblinded at the subject level. This will be performed using the associated "-clinical" folder.

"prot028-ia-sumamry" folder in the PROD region

After the database lock for the interim analysis is achieved, the unblinded statistician and the unblinded statistical programmer will post group level summary results to this folder for review by the project team. The protocol statistician will prepare the Early Results Memo based on the group level summary results using the tables posted in this folder.

It is the responsibility of the unblinded statistician to mask or remove part of the output before providing the output with the project team in order to avoid potential subject level unblinding. Examples include:

- AEs, disposition events, medical history, prior / concomitant medications observed in only one participant or in only one vaccination group
- minimum and maximum (e.g., baseline body weight).